Synthetic approaches to methaniminomethanophenanthrenes.

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SYNTHETIC APPROACHES TO

METHANIMINOMETHANOPHENANTHRENES.

submitted by PAUL BIRD

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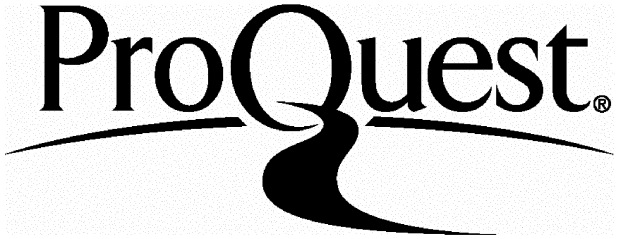
1982



To my parents.

ACKNOWLEDGEMENTS

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ABSTRACT

Synthetic approaches to (methaniminomethano)phenanthrenes have been discussed and investigated.

Routes to 4-(3,4-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,4-dihydro-3(2H)-isoquinolone have been established, but the electrochemical oxidation of this substrate yielded only polymeric material. Similarly a synthesis of 2-formyl-1,2,3,4-tetrahydro-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)isoquinoline was completed and its electrochemical oxidation investigated.

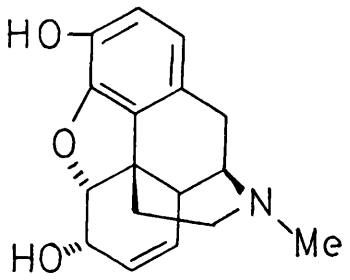
A series of 2,3-diphenylpropionamides were synthesised and oxidised using vanadium trifluoride oxide; 2-(2-acetoxy-methyl-3,4-dimethoxyphenyl)-3-(3,4-dimethoxyphenyl)propionamide (I) produced 10,11-dihydro-5,11-(iminomethano)-2,3,7,8-tetramethoxy-5H-dibenzo[a,d]cyclohepten-12-one (II) and 11-carboxamide-10,11-dihydro-2,3,7,8-tetramethoxy-5H-dibenzo[a,d]cycloheptene; the corresponding 2-(2-benzyloxymethyl-3,4-dimethoxyphenyl) derivative of (I) also produced (II); the N-methyl derivative of (I) yielded 2,3,6,7-tetramethoxy-N-methylphenanthrene-9-carboxamide.

The structure of the electrochemical product of 4-(3,4-dimethoxybenzyl)6,4-dimethoxyisochroman-3-one (III) was investigated and was shown to be 9,8a-carbonyloxymethano-6,8a,9,10-tetrahydro-2,3,7-trimethoxy-6-oxophenanthrene (IV). The product (IV) was converted into a series of intermediates aimed at the novel 8a,9-(methaniminomethano)phenanthrene ring system.

CONTENTS

Introduction

The principal alkaloid of the opium poppy Papaver somniferum, morphine (1)[1] occupies an important central position in the field of medicinally valuable natural products.



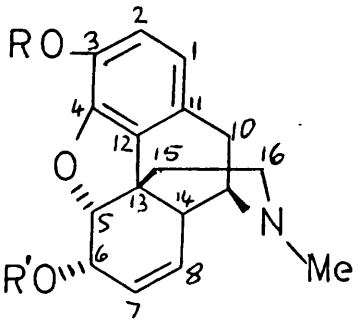
(1) morphine.

The ability of morphine, in its crude form as the drug opium, to relieve pain has been known for many centuries[2], yet only in comparatively recent times has morphine been isolated and identified[3]. The use of morphine is now restricted to patients who are suffering with severe pain, as the unfortunate side effects can be very destructive[4]. These effects include nausea, vomiting and constipation at low dosage levels, while increased administration causes respiratory depression, reduced blood pressure and heart rate. Continued usage causes both physical and mental dependence. The search for a drug with powerful analgetic properties but devoid of the side-effects of morphine has been the subject of much research, and as yet no such drug has emerged[5].

Modification of the morphine structure

The complex structure of morphine (1) has allowed certain chemical modifications which have in turn caused a change in the analgetic properties. Thus acetylation of the two hydroxyl groups forms heroin (2), which has a slightly greater analgetic potency, but a much higher addictive profile.

Selective methylation of the phenolic hydroxyl group produces the milder analgetic codeine (3) which is much less addictive. Correspondingly methylation of the 6-hydroxyl group causes an increase in analgetic activity[5], but the derivative formed is still a narcotic agent and not a useful drug.



(1, R = R' = H, morphine)

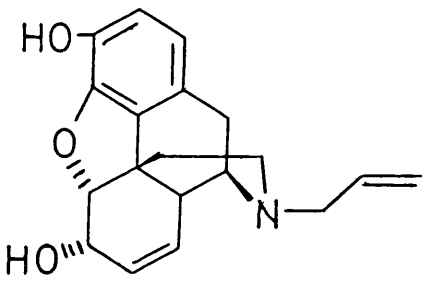
(2, R = R' = Ac, heroin)

(3, R = Me, R' = H, codeine)

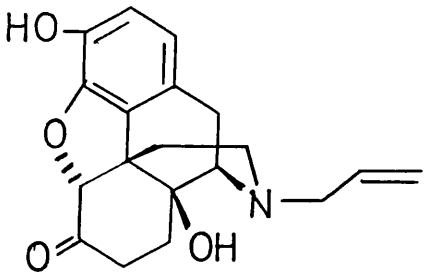
The removal of the double bond usually results in a doubling of the pain killing activity, whereas if the cyclic ether is reduced an almost complete loss of activity[6] is observed.

Replacement of the N-methyl substituent has a marked influence upon the activity of drugs of the morphine series. Replacement by the 2-phenylethyl group leads to about an eight fold increase in analgetic potency[7]. In connection with these and other drug modification studies the terms antagonists and agonists are often used; it is thought that the role of antagonists is that they compete with agonists for receptor sites within the central nervous system. Here instead of causing a pharmacological effect, as do agonists, they simply block the site and inactivate it.[12]

Pure opiate agonists can be converted into partial antagonists by replacement of the N-substituent with either N-cyclopropylmethyl, or N-allyl groups[8]. The N-allyl group produces a compound nalorphine (4) which is as active as morphine, but again has harmful side effects especially towards the brain. Nevertheless this compound is used as an antagonist in narcotic overdose treatment since it is non-addictive and alleviates respiratory depression normally caused by morphine.



(4, nalorphine)



(5, naloxone)

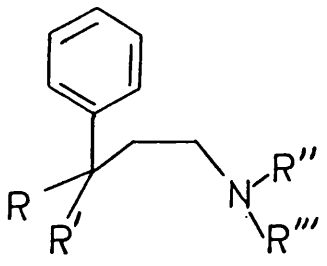
A compound related to nalorphine (4) which is devoid of many of the harmful mental side effects is naloxone (5), this is the most potent pure antagonist known[9,10]. A recent proposal[11] is that a mixture of naloxone (5) and methadone, a simple relative of the morphines (see p. 6), should be used in humans, thus the antagonist could block the euphoria produced by methadone without interfer ing with the analgetic effect.

Compounds with part of the morphine structure

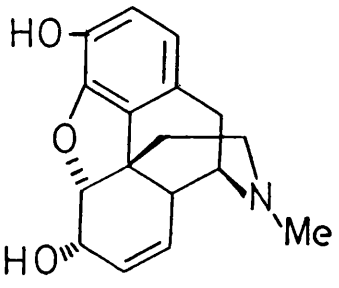
In the following section compounds which have part of the morphine structure will be considered and the structural requirements for activity within the series explored.

Eddy[13,14] introduced a concept of structural features necessary for analgetic activity these being:

(a) an aromatic ring attached to a quaternary carbon centre, and
(b) a tertiary nitrogen situated two carbons distant from the quaternary carbon. This relationship is depicted as the "Eddy model" (6), a comparison with morphine (1) can be readily appreciated.



(6, "Eddy model")



(1, morphine)

A number of structures fit the Eddy requirements and the classes of synthetic analgetics based upon the "Eddy model" can be grouped within the following categories:

(a) Substituted propylamines.

(b) Cyclic amines

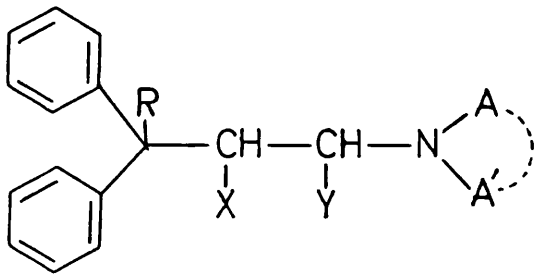
(c) Benzomorphans

(d) Morphinans

(e) Miscellaneous compounds

(a) Substituted propylamines

This class is based upon the simplest form of the "Eddy model" (6). The largest group of compounds in this class is the 3,3-diphenyl propylamines[15] which have the general structure (7).

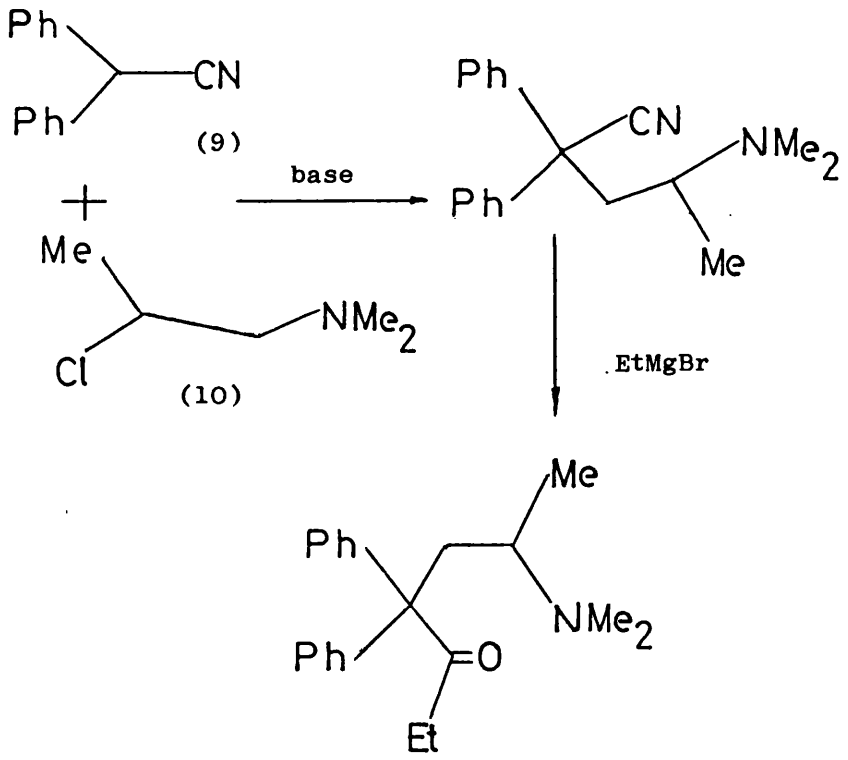


(7)

Considerable effort has been devoted to the development of this system and as a result a myriad of compounds have been synthesised[15]. The substituent R can be hydrogen or almost any functional group e.g. hydroxyl, alkyl, nitrile, ester, amide etc., X and Y tend to be either hydrogen or

simple alkyl groups. A and A' usually are simple alkyl groups or may be a bridged system forming a simple nitrogen heterocycle.

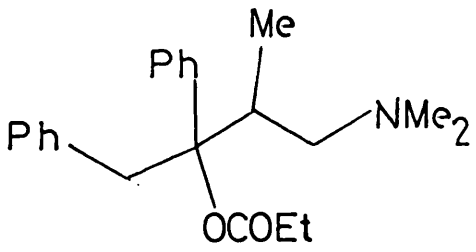
An example of this type of compound is methadone (8)[16], which was first synthesised in 1948 by Bockmuhl and Ehrhart[17]. Their route employed the condensation of diphenylacetonitrile (9) and 2-chloro-N,N-dimethylpropylamine (10), followed by a Grignard reaction with ethyl magnesium bromide this formed the desired amine, methadone (8)[17,18].



(8, methadone)

Methadone (8) has found use in the treatment of morphine based addicts in North America[19,20] as well as being used as an analgetic in its own right.[15]

Another example of a substituted propylamine is propoxyphene (11) which is claimed to be an analgetic[21] with an equivalent potency to codeine (3)[22].

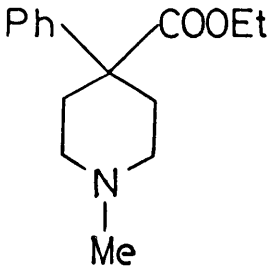


(11, propoxyphene)

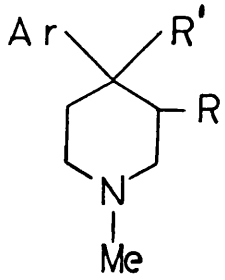
(b) Cyclic amines

This class of analgetics includes the cyclic amines which are not classified in the other classes, it mainly contains the two types based on either piperidines or pyrrolidines sub-structures. The structural relationship between morphine and 4-phenyl piperidines was noted by Schaumann as long ago as 1940[23].

The same author was also responsible for the synthesis of pethidine (meperidine) (12)[24], which has a quarter of the pain killing action of morphine[25].

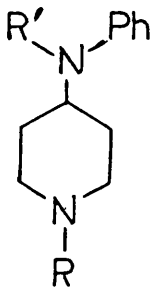


(12, pethidine)



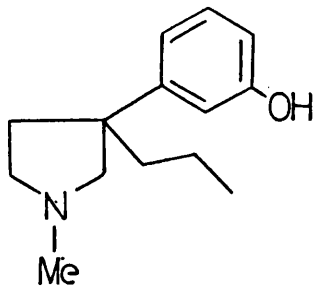
(13)

The structural-activity correlations for the pethidine ring system (13) have been investigated on numerous occasions. For example replacement of the aryl group, Ar, by 2-pyridyl or 3-thienyl in the R' = OCOEt series gives retention of analgetic activity[26]. If R = Me, in either of the R' = COOEt or R' = OCOEt series the resultant compounds are active analgetics[27], but replacement of R = Me by a halogen destroys the activity[28]. The 4-anilinopiperidines (14) have also been synthesised and their structure-activity relationships have been extensively investigated[29].

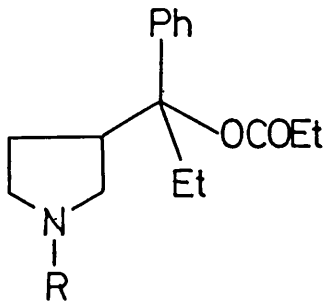


(14)

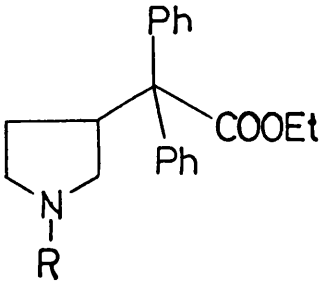
There are a number of pyrrolidine derivatives which also show analgetic activity and as with the piperidines these adhere closely to the "Eddy model" (6). Profadol (15) has been shown to have about one quarter of the pain killing action of morphine in post-operative[30] and in cancer patients[31]. Esters of 3-pyrrolidinemethanols e.g. (16) and (17) generally exhibit a level of analgetic activity similar to propoxyphene (11)[32,33]. Analogous structures such as 3-pyrrolidinyl-anilides, for example (18), are more active, with three times the potency of morphine, but show undesirable side effects[34].



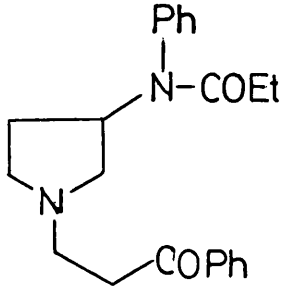
(15, profadol)



(16)

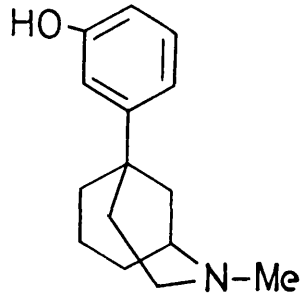


(17)



(18)

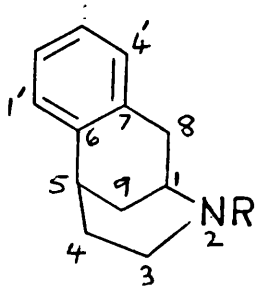
Another cyclic amine within the framework of the "Eddy model" (6) is the compound 5-(3-hydroxyphenyl)-2-methylmorphan (19), which along with other compounds in this series is an analgetic[35] with a pain killing activity equivalent to morphine[35].



(19)

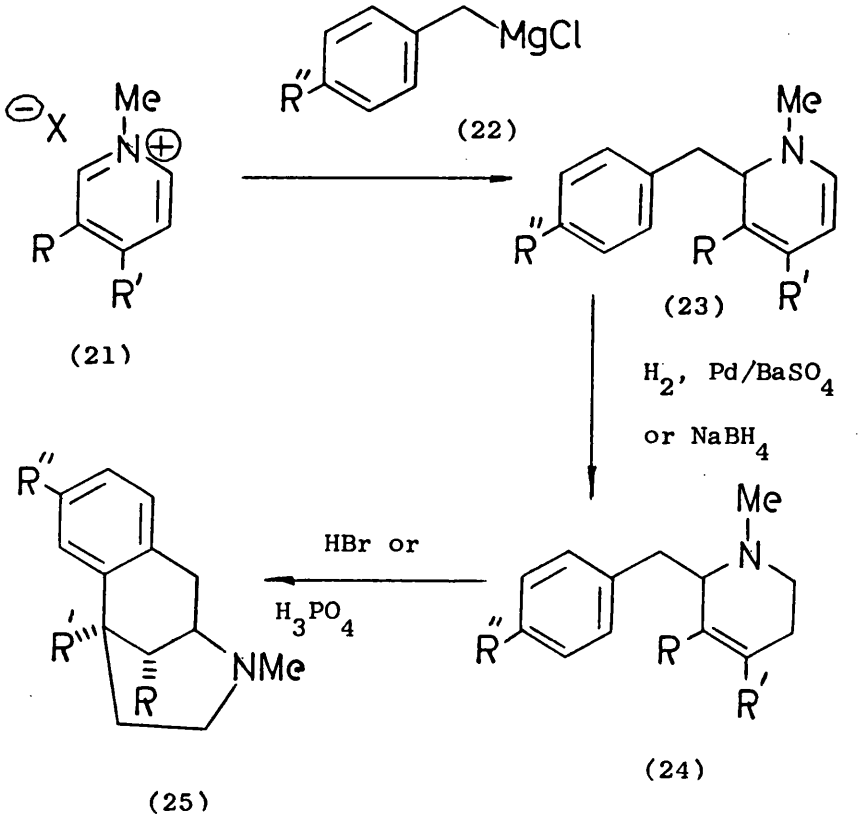
(c) 6,7-Benzomorphans

If the morphine structure is modified such that ring C is omitted, the new system created is called a 6,7-benzomorphan (20).

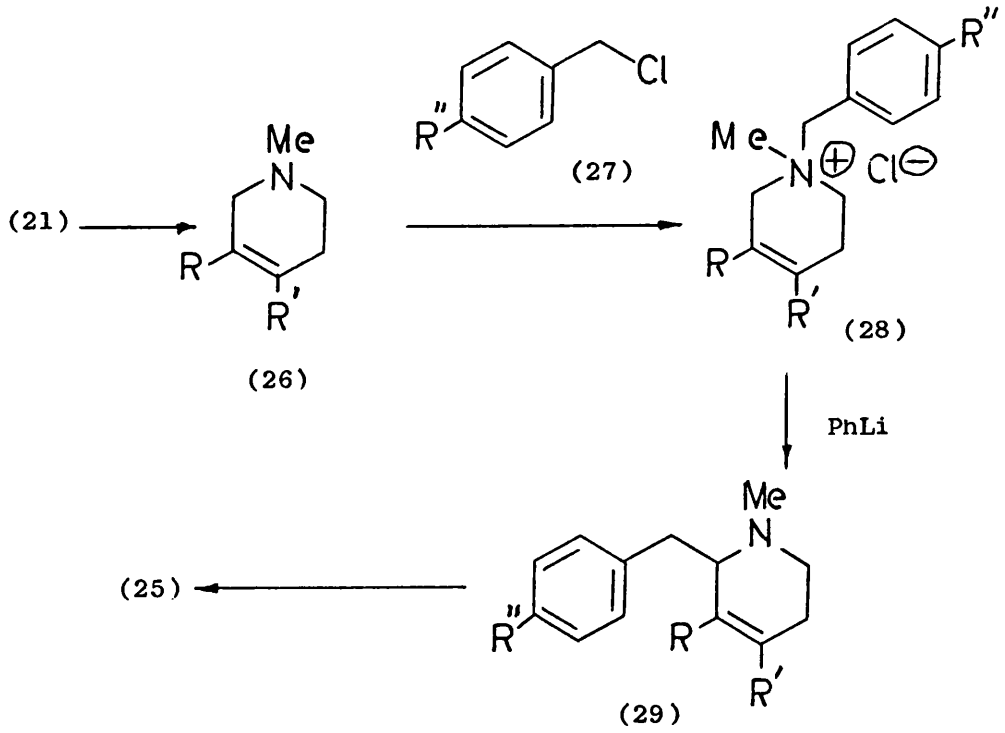


(20, 6,7-benzomorphan)

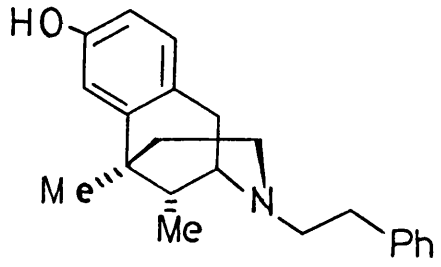
Many benzomorphans have been synthesised by a number of routes[36] some are useful others less so, two of the best procedures are considered here. Thus, May[37] developed the following general approach from the pyridinium salt (21), this was treated with the benzyl Grignard reagent (22) to form the rather unstable dihydro pyridine (23). Reduction of the pyridine (23) could be carried out either by hydrogenation with palladium on barium sulphate or preferably with sodium borohydride to yield the tetrahydropyridine (24). The final step in this sequence consisted of an acid catalysed Grewe[38] cyclisation of the pyridine derivative (24) using either hydrobromic acid or phosphoric acid to afford the benzomorphan (25).



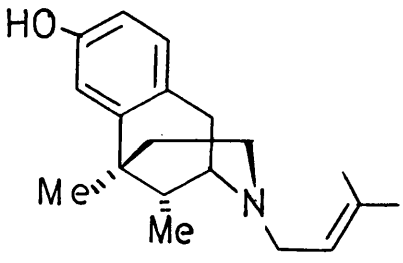
An alternative approach[39,40] to the benzomorphan (25) again starts from the pyridinium salt (21) which was reduced to the tetrahydropyridine (26). Quaternization of the pyridine (26) with the <u>para</u>-substituted benzyl chloride (27) formed the salt (28) which was then treated with phenyl lithium causing a Stevens rearrangement[41] to the tetrahydropyridine (29). The pyridine (29) was again cyclised by acid, as in the previous route, to the benzomorphan (25).



The first of the benzomorphans to be used as an analgetic was phenazocine (30), which was first synthesised in 1959 by May[42]. Later came the analgetic drug pentazocine (31)[43]. Structural features which enhance pain killing potency include: a hydroxyl group at position 2' in the aromatic ring, simple alkyl groups at positions 5 and 9. Variations in the N-substituent also cause differing potency, the N-methyl series is active, while the N-ethyl series tend to be inactive. An increase in N-alkyl length restores the analgetic activity in the order N-propyl > N-amyl > N-hexyl > N-phenethyl > N-phenacyl[44]. Even the unsubstituted series shows analgetic activity[45].



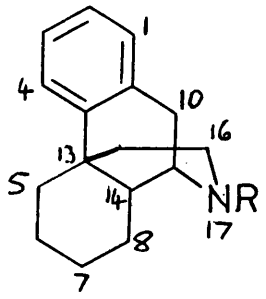
(30, phenazocine)



(31, pentazocine)

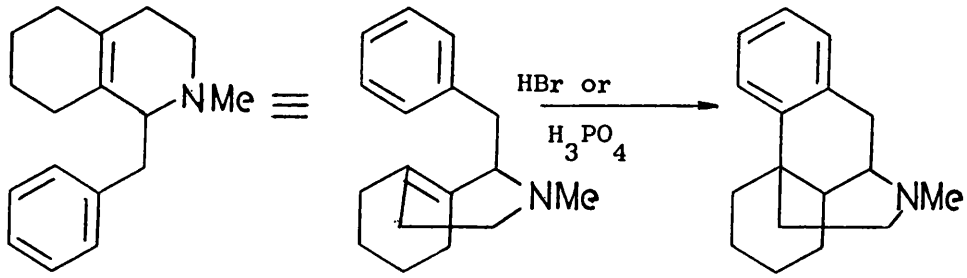
(d) Morphinans

This class of analgetics retains the whole of the basic morphine skeleton but without the 4,5-oxygen bridge; the general structure and numbering is shown in the morphinan (32).



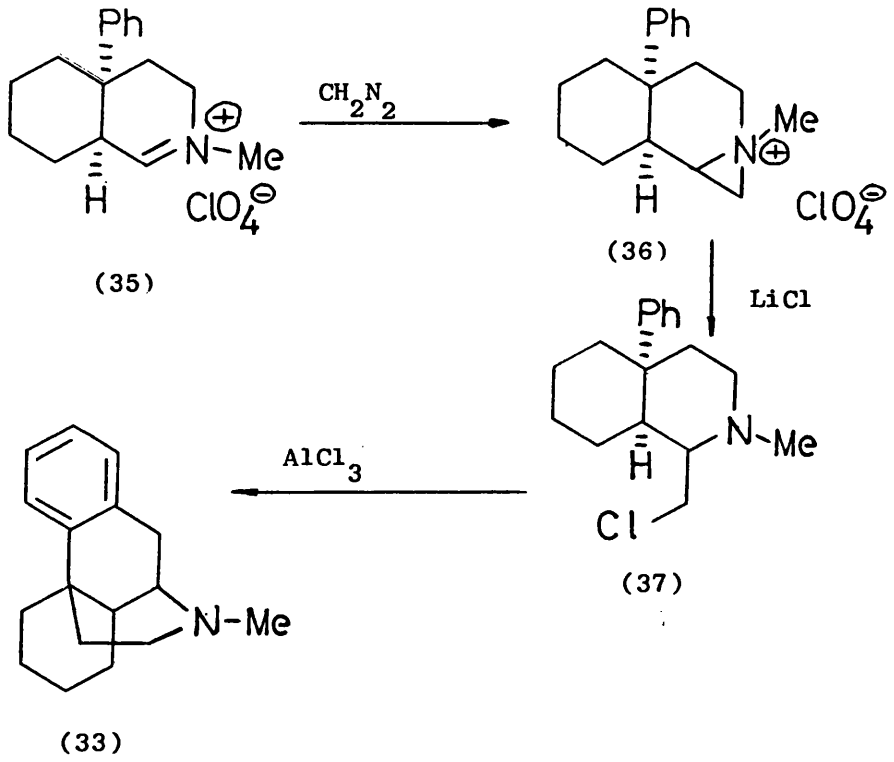
(32, morphinan)

N-methylmorphinan (33) was first synthesised in 1948 by Grewe and Mondon[38,46,47], from the octahydroisoquinoline (34). Cyclisation was effected by strong acid, and has been termed the Grewe cyclisation.



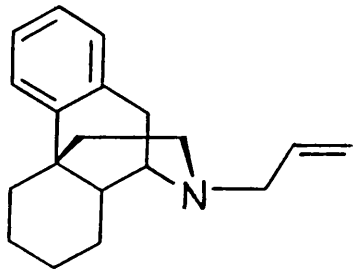
(34) (34) (33)

The N-methylmorphinan (33) has been recently synthesised by Evans[48], this route involved the iminium salt (35) which is converted to the aziridinium salt (36) by reaction with diazomethane. The aziridine ring is then opened by lithium chloride to the alkyl chloride (37), and the target morphinan (33) then formed by an intramolecular Friedel-Crafts alkylation.



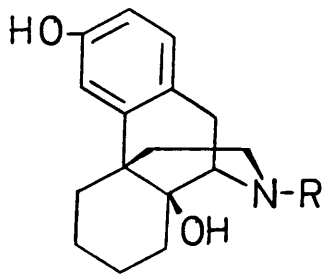
Considerable synthetic effort has been directed towards the morphinan system and many syntheses have appeared[49] producing a range of compounds with various analgetic profiles[49].

The morphinan (33) has about one-fifth the analgetic activity of morphine (1). An interesting similarity between this type of ring system and morphine is that their biological properties are dependent upon the N-substituent. For example, the N-allyl derivative (-)-levallorphan (38) is an antagonist, which is more than twice as effective as nalorphine (4)[50].



(38, levallorphan).

The morphinan group continues to generate interest[51] and the corresponding 3,14-dihydroxymorphinan N-substituted derivatives (39)[52], (40)[53], (41)[54], have also been shown to have interesting pharmacological properties.



(39, R = $-CH-CH=CH_2$)

(40, R = $-CH_2$)

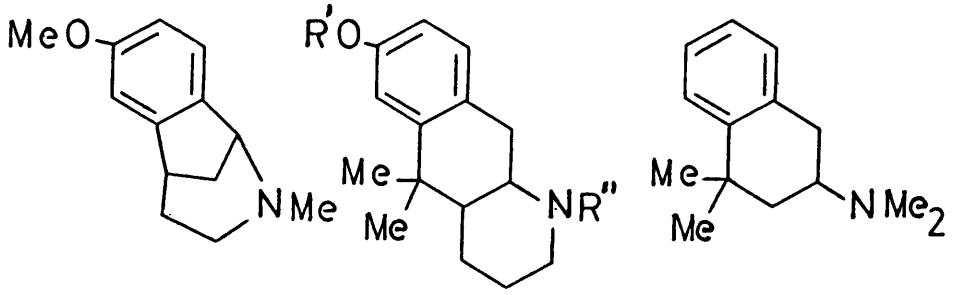
(41, R = $-CH_2$  , butorphanol)

Butorphanol (41) is now in clinical use and is claimed to be non-addictive as well as being ten times more potent than morphine as an analgetic agent in man[55].

(e) Miscellaneous compounds

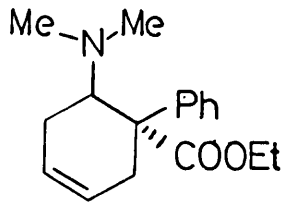
In this section are grouped various compounds which have analgetic properties but are not classified under the previous headings.

The B-norbenzomorphan (42) is similar in analgetic potency to codeine[56]. Weak narcotic antagonist activity has been found in the series of N-substituted octahydrobenzquinolines (43)[57], while the related 2-dimethylaminotetralin (44) shows two and a half times the analgetic potency of pethedine (12)[58].

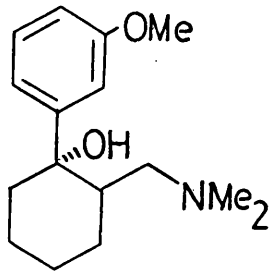


(42) (43) (44)

The cyclohexene (45)[59] has morphine-like activity while the cyclohexane derivative (46)[60] is somewhat less potent.



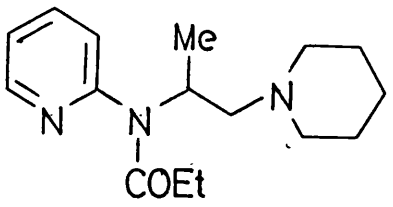
(45)



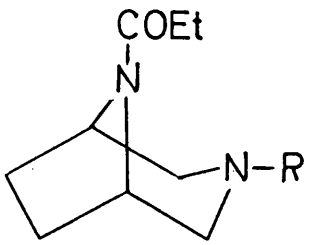
(46)

The basic anilide Propiram (47)[60] is a weak morphine antagonist in man, with only one-fifth of its activity.

The diazabicyclo[3,2,1]otane (48)[61] is a mild analgetic in man, whereas the 3-cinnamyl derivative (49)[62] is several times more potent than morphine.



(47, Propiram)



(48, R = Me)

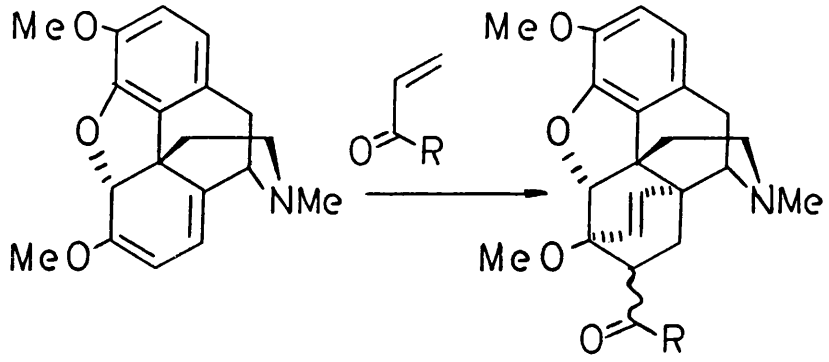
(49, R = CH_2.CH = CHPh).

Compounds more complex than morphine

The previous cases of synthetic analgetics all are based upon a simplification of the morphine structure by major or minor modifications, this work depends upon the belief that the features incorporated are those responsible for the analgetic action and further complexity is unnecessary and undesirable[63]. Thus in 1967, Bentley[64] proposed that the simple analgetic compounds were more flexible than the morphine structure and could be easily accepted into the morphine receptor sites. The result of this was that structure-activity relationship studies were hampered because the lack of rigidity to provide a model which allowed the separation of those features responsible for the desirable analgetic properties and those which caused the undesirable side effects.

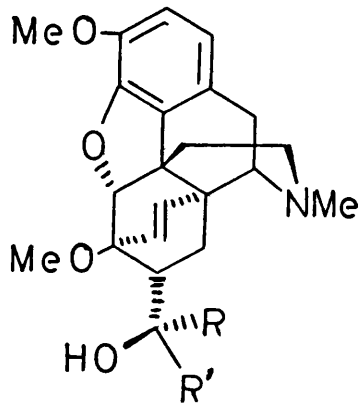
In an attempt to separate these effects Bentley[64] synthesised compounds that were more complex than morphine(1), more rigid and with a different peripheral shape. The point of this approach was to reduce their availability to certain sites of the receptor surfaces, so that the development of a "lock and key" theory could take place as the stereochemistry of each drug was related to its biological effect.

Initially Bentley[64] reacted various α,β-unsaturated ketones with thebaine (50) forming Diels-Alder adducts - 6,14-endo-ethenotetrahydrothebaines (51) - which had a range of activities in the central nervous system. Some of these compounds proved to be more potent analgetics than morphine and it is worth noting that thebaine (50)itself has no analgetic properties.



(50, thebaine) (51)

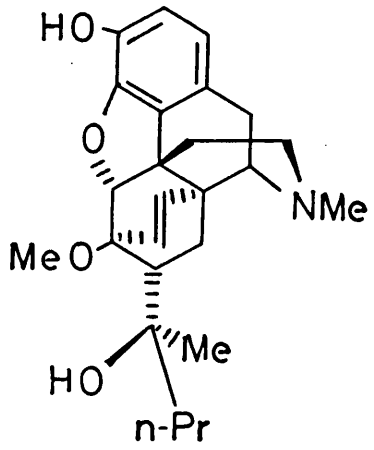
It was found[65] that the adducts (51, R = H, Me, Et, n-Pr and Ph) could be converted into a series of alcohols either by reduction or by reaction with Grignard reagents to produce stereospecifically compounds of general structure (52). Some of these products are up to five hundred times more potent than morphine as pain killers.



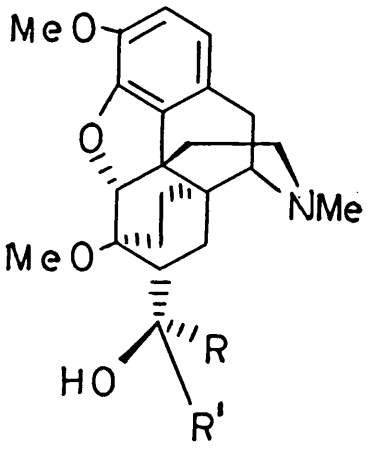
(52)

Selective demethylation of the aryl ether in this series produces a group of compounds termed oripavines, which are extremely active[66]. The oripavine, etorphine (53)[67,68] is used in veterinary medicine for the immobilisation of wild game, and has an activity ten thousand times more potent than morphine[66].

Reduction of the 6,14-endo-etheno bridge in compounds of the type (52) yields the corresponding 6,14-endoethano derivatives (54)[65] which have slightly increased activity over their alkene precursors.



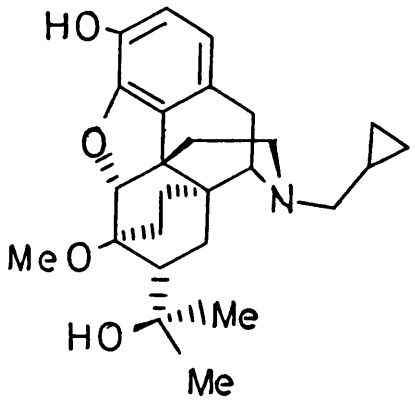
(53, etorphine)



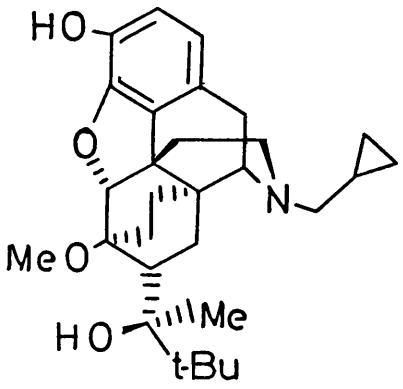
(54)

Replacement of the N-methyl substituent in the 3-hydroxy-6,14-endoethano series creates compounds with antagonist properties[66]. Examples of this type of system are diprenorphine (55), which is used as a specific etorphine (53) antagonist[69],

and buprenorphine (56) which is a powerful analgetic in Man[69]. Buprenorphine (56) has recently been introduced as the drug Temgesic in the United Kingdom[70].



(55, diprenorphine)



(56, buprenorphine)

Buprenorphine (56) has a low addictive profile and has the unusual ability to antagonise its own action at higher dosage, hence preventing to some extent, the danger of overdosage[69]. Of all the work summarised in this introduction the work on buprenorphine seems the most important although drug companies still spend considerable sums in the search for the ideal analgetic.

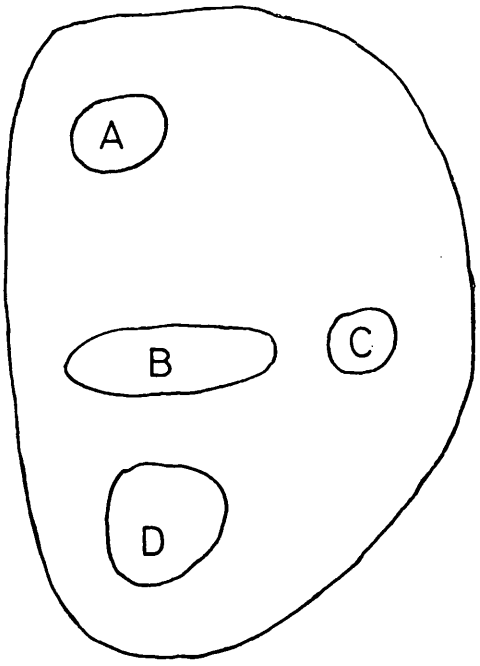
The Analgetic Receptor site

Drug design based upon the morphine skeleton as discussed above, has been founded upon general structural similarities between the parent molecule and its analogues. From this work developed an empirical analysis of the nature of the receptor site. The earliest model postulated by Beckett and Casy[71] in 1954, was based upon a three point fit for the "morphine drug" and was by implication stereoselective in keeping with the general observation that in analgetics containing a chiral centre one enantiomer is always more active than the other[72].

The Beckett and Casy[71] model is simply a diagrammatic representation of an area on an enzyme or its equivalent which allows the accommodation of the following features of the drug (a) an aromatic A ring (b) a cavity to accept the ethano bridge (i.e. C-15 and C-16 of morphine) and (c) an anionic site which can bind to the nitrogen atom which is normally protonated at physiological pH.

In 1971 Lewis[60] extended the model to include a lipophilic site which could then be used to explain the potency of the oripavines and 6,14-endoethenotetrahydrothebaines. A crude diagrammatic representation of this model can be depicted

as shown below.



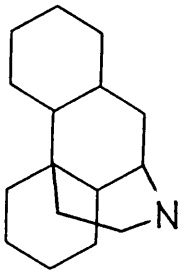
The Bentley-Lewis model of the morphine receptor.

A-flat region associated with the A-ring (aromatic ring), B-cavity for the C-15 and C-16 ethano bridge, C-anionic site for protonated nitrogen atom, D-lipophilic site for C-7 side chain of the "Bentley adducts" and oripavines.

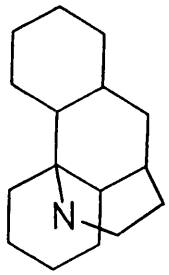
While the crude model has obvious flaws and limitations it has served as a rough guide to synthetic organic chemists striving to produce the ideal analgetic. Some of these attempts are now summarized although such is the volume of this work that only a very limited survey is possible here, and this is largely polarised in the direction of the work which is to be described later in the discussion section.

Synthesis of the Isomers of morphine

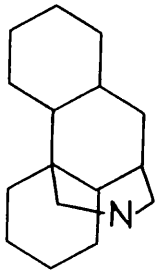
The morphine ring system has been the template for many approaches to synthetic drugs, other attempts at producing analgetics with modified action have been directed towards the isomers of morphine in which the position of the nitrogen atom in the ethanamine bridge is varied. Thus there have been three main targets (a) derivatives of the morphinan system, 10,4a-(iminoethano)phenanthrenes itself, (57), (b) 4a,10-(iminoethano)phenanthrenes (58), and (c) 4a,10-(methaniminomethano) phenanthrenes (59).



(57)



(58)



(59)

a. Synthesis of 10,4a-(iminoethano)phenanthrenes (57)

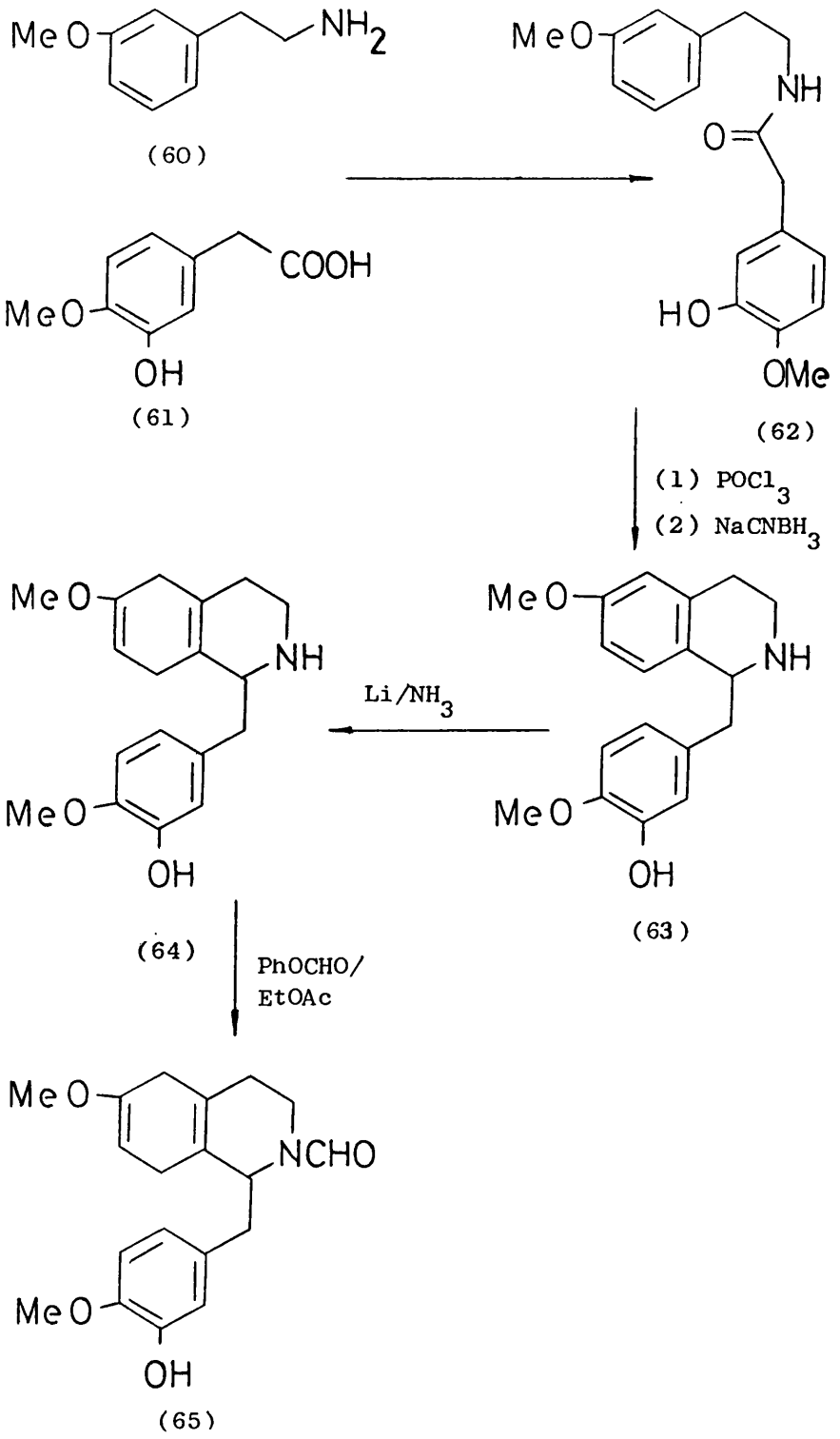
Since the isolation of morphine[3] (1), there have appeared many syntheses of the 10,4a-(iminoethano)phenanthrene (57) ring system. Morphine (1), itself being first synthesised in 1952 by Gates[73], this work has gone on over the years and just recently a synthesis of precursors to morphine was presented by Rice[74]. Other syntheses have included major studies by Kametani[75], Grewe[76], Morrison[77], Beyerman[78], Barton[79] and Schwartz.[80]

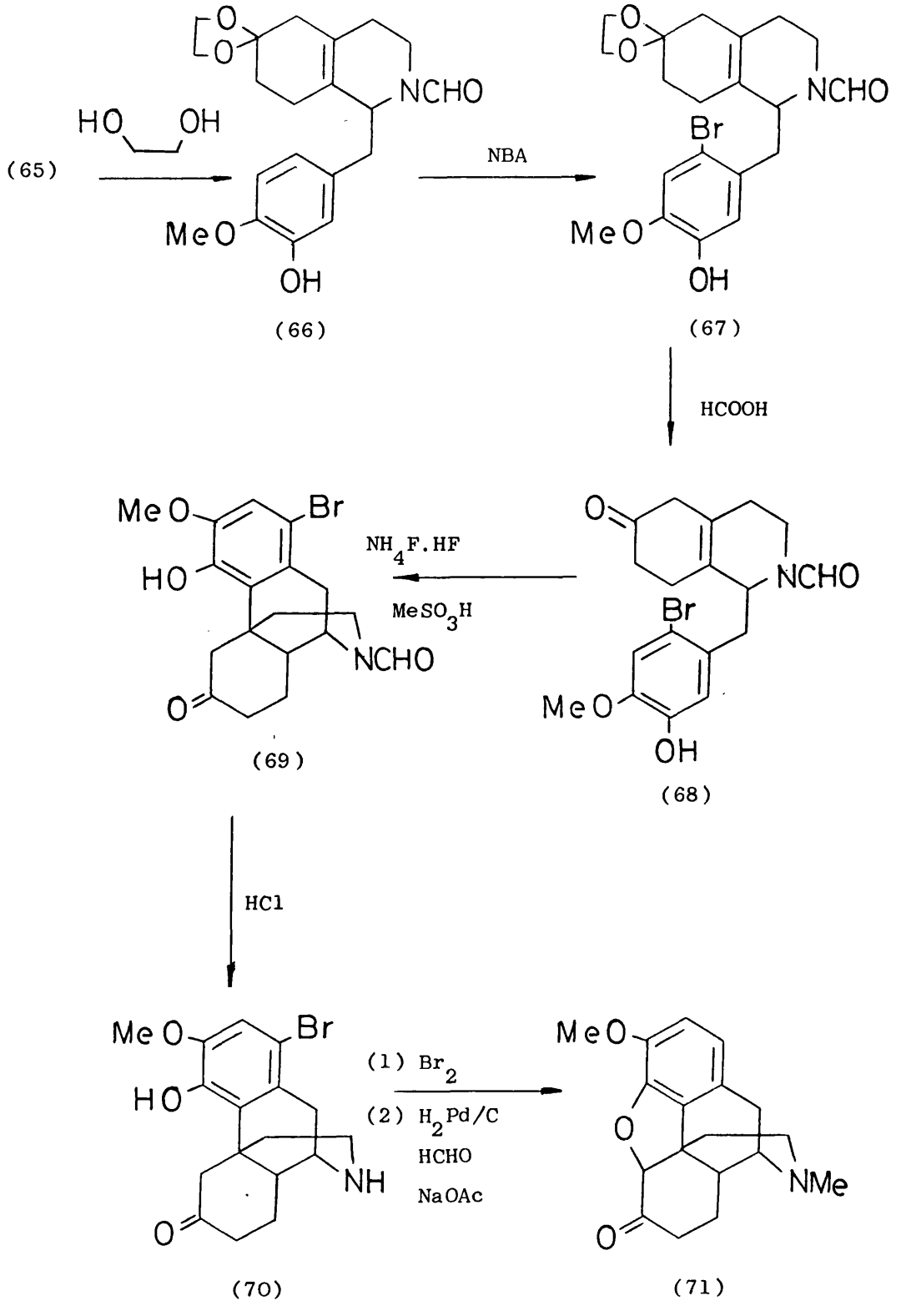
The Rice[74] route starts with a condensation of the amine (60)[87] and the acid (61) to form the amide (62). The amide (62) was then cyclised, using the Bischler-Napieralski reaction[81,82], by the action of phosphorus oxychloride ($POCl_3$) and the intermediate 3,4-dihydroisoquinoline reduced *in situ* by sodiumcyanoborohydride ($NaCNBH_3$) to give the tetrahydroisoquinoline (63). The isoquinoline (63) was reduced using the Birch[83] conditions, i.e. lithium in ammonia, to afford the hexahydroisoquinoline (64).

N-Formylation[84] of this product gave the amide (65) which was selectively hydrolysed by acid and the intermediate ketone protected as the acetal (66) using ethylene glycol. Treatment of the acetal (66) with N-bromoacetamide (NBA) formed the bromoacetal (67) which was deprotected using dilute formic acid thus yielding the bromoketone (68). When this was treated with ammonium fluoride/hydrogen fluoride in dry methane sulphonic acid, a Grewe type cyclisation[38] occurred forming 1-bromo-N-formylnordihydrothebainone (69). The N-formyl group was hydrolysed off by methanolic hydrochloric acid treatment giving the amine (70), which was brominated using bromine in acetic acid, and then the product immediately hydrogenated over palladium on charcoal in acetic acid containing sodium acetate and formaldehyde, to form the dihydrocodeinone (71).

Since Rapoport[85] had already published a method of converting dihydrocodeinone (71) to codeine (3) and the O-demethylation of the latter to morphine (1) is a known process[86],

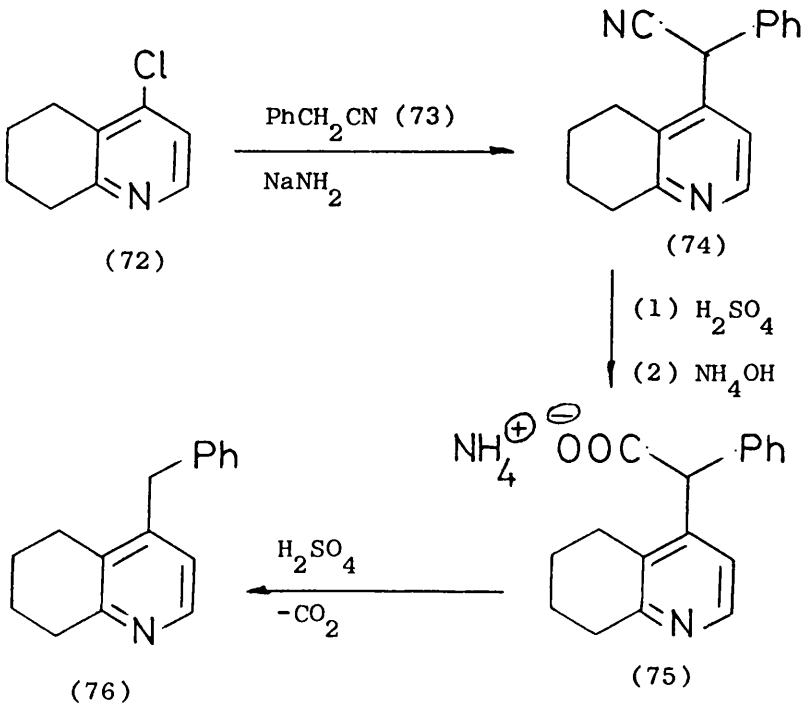
Rice had successfully completed a total synthesis of morphine as well as many of the important morphine alkaloids.

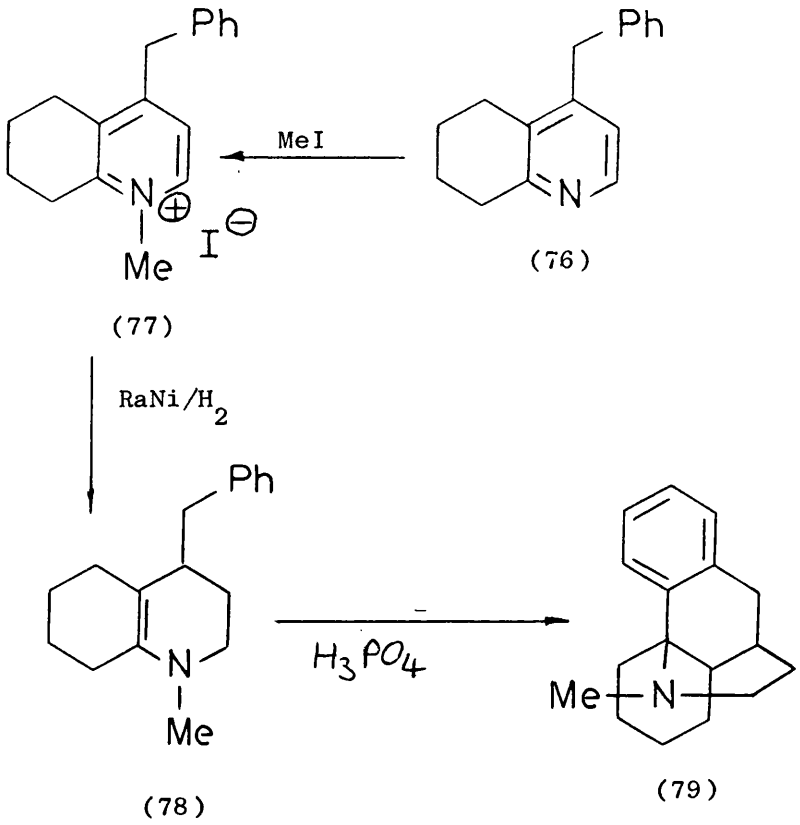



(65)
HO OH
NBA
NCHO
MeO
OH
Br
(66)
(67)
HCOOH
(68)
NH4F.HF
MeSO3H
(69)
HCl
(70)
(1) Br2
(2) H2Pd/C
HCHO
NaOAc
NH
NMe
(71)

b. Synthesis of 4a,10-(iminoethano)phenanthrenes (58)

The 4a,10-(iminoethano)phenanthrene ring system is poorly represented in the chemical literature, although it was first synthesised in 1955 by Ochiai and Harasawa[88]. These workers started their sequence with 4-chloro-5,6,7,8-tetrahydroquinoline (72) which was reacted with the anion generated from benzyl cyanide (73) to give the 4-substituted quinoline (74). Hydrolysis of the nitrile unit of this product, followed by quenching with ammonium hydroxide, yielded the ammonium salt (75), which was thermally degraded to the 4-benzyl quinoline (76). Quaternisation with methyl iodide afforded the salt (77) and this was then hydrogenated over Raney nickel catalyst to yield the octahydroquinoline (78). An acid catalysed cyclisation of this product using phosphoric acid as the reagent formed the desired ring system, the actual compound produced being called N-methylallomorphinan (79).

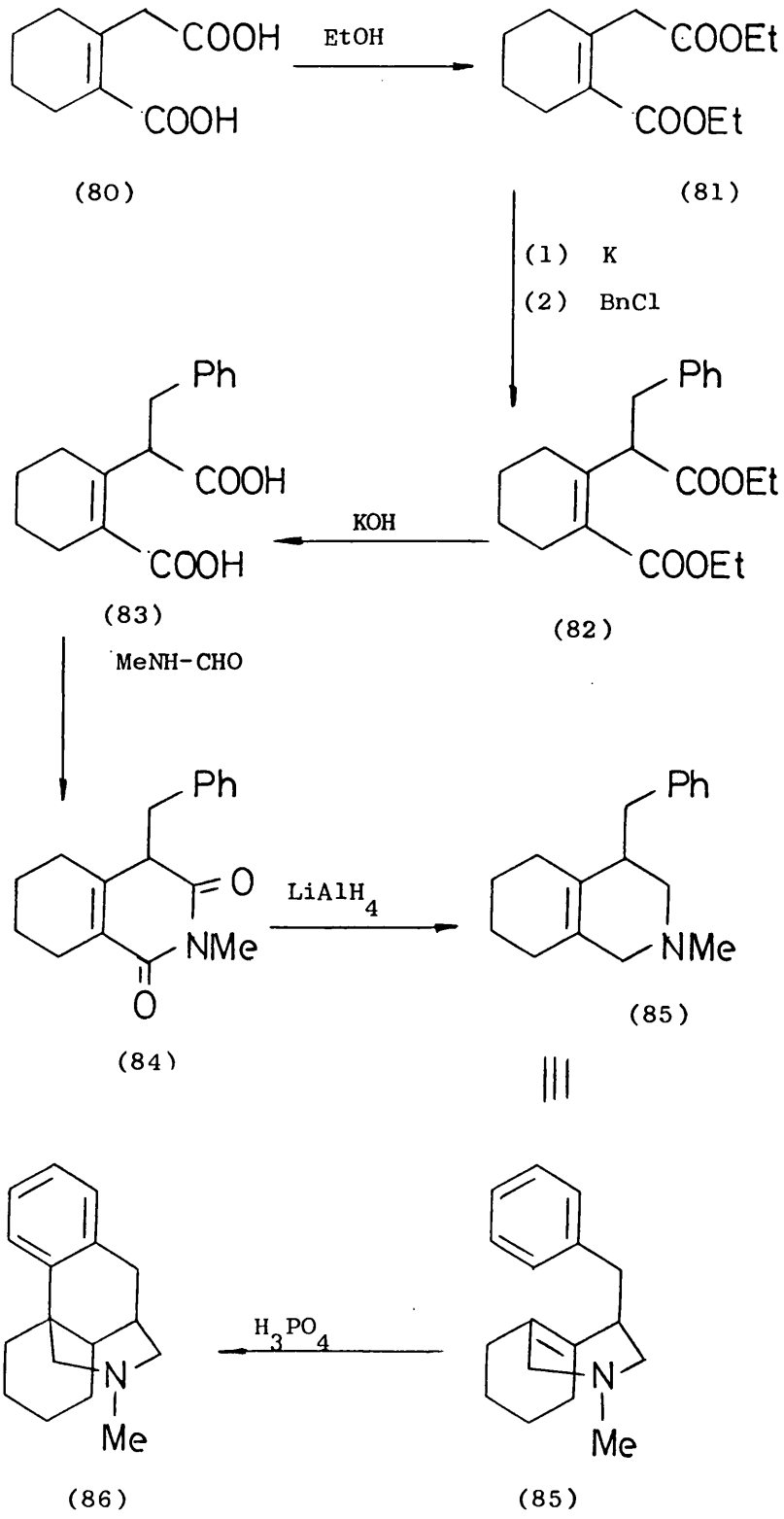




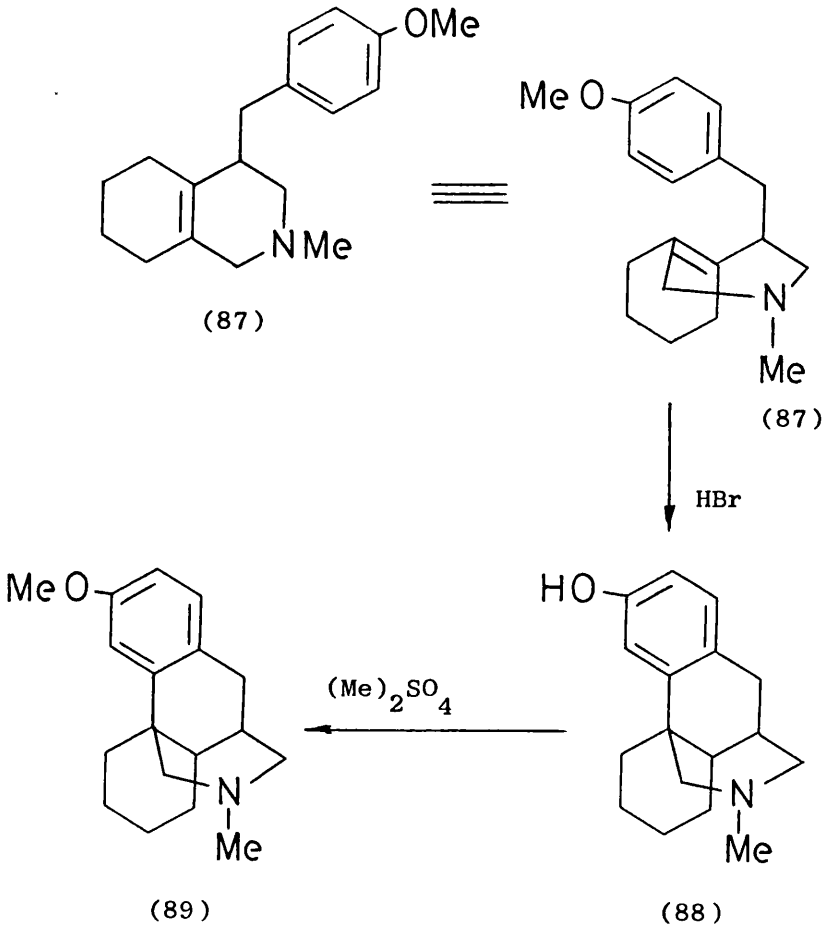
c. Synthesis of 4a,10-(methaniminomethano)phenanthrenes (59)

This ring system is also rather uncommon, the first synthesis being described by Sugimoto[89] in 1956. The starting point was the diacid (80) which was first esterified to the diester (81). The potassium salt of the ester (81) was then reacted with benzyl chloride to form the benzyl derivative (82), hydrolysis using potassium hydroxide gave the diacid (83). On heating with methylformamide the diacid (83) afforded the imide (84) which was reduced by lithium aluminium hydride to form the octahydroisoquinoline (85). The target ring system

was produced by an acid catalysed cyclisation using phosphoric acid as reagent. This treatment yielded the 4a,10-(methanimino-methano)phenanthrene (86).



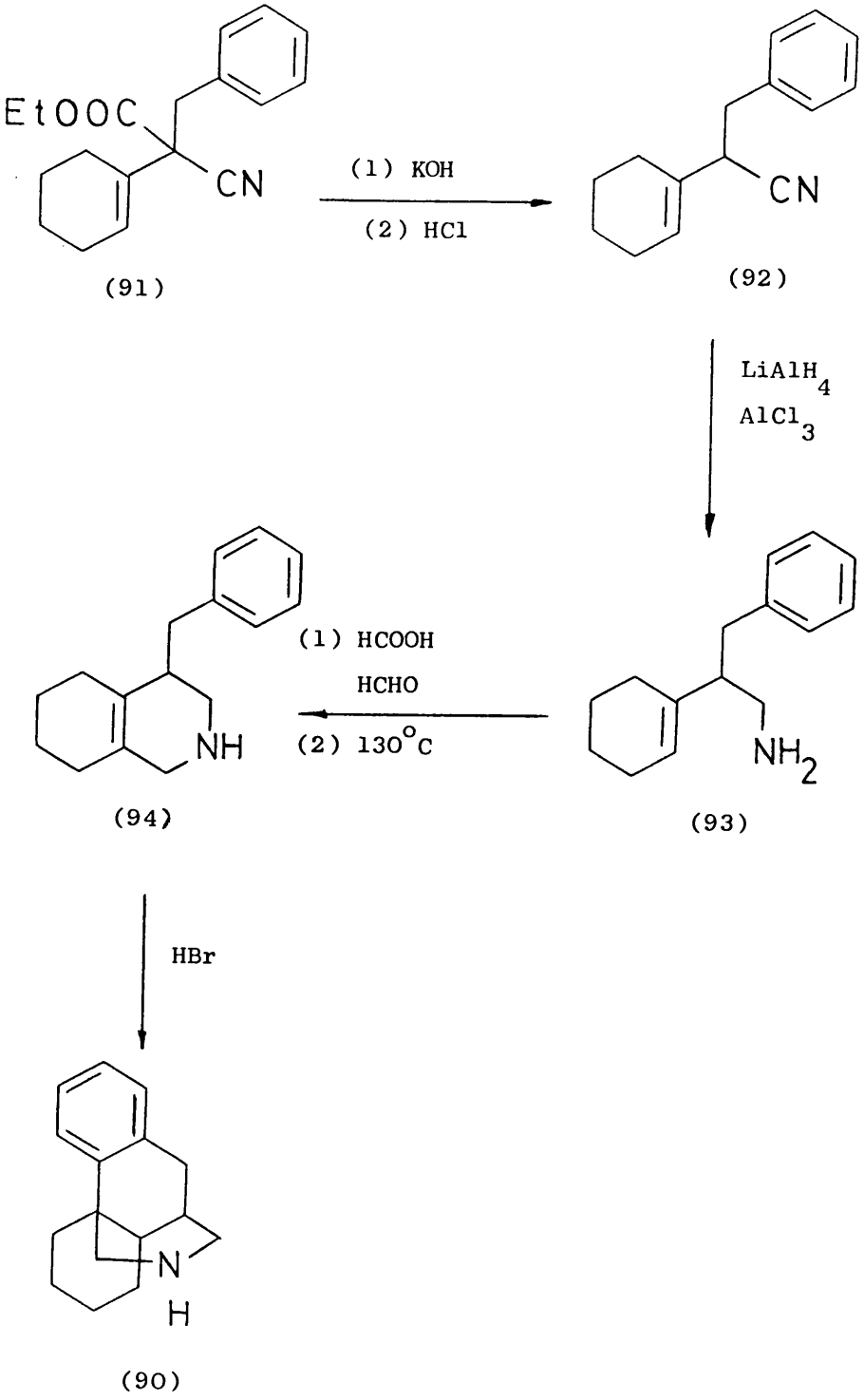
Sugimoto[90] also cyclised the corresponding <u>para</u>-methoxy derivative (87) using hydrobromic acid as the catalyst. This gave the phenol (88) which was methylated with dimethylsulphate to form the ether (89). These compounds were reported to have no analgetic properties[90], although two patents were published based upon the results of this work[91,92].



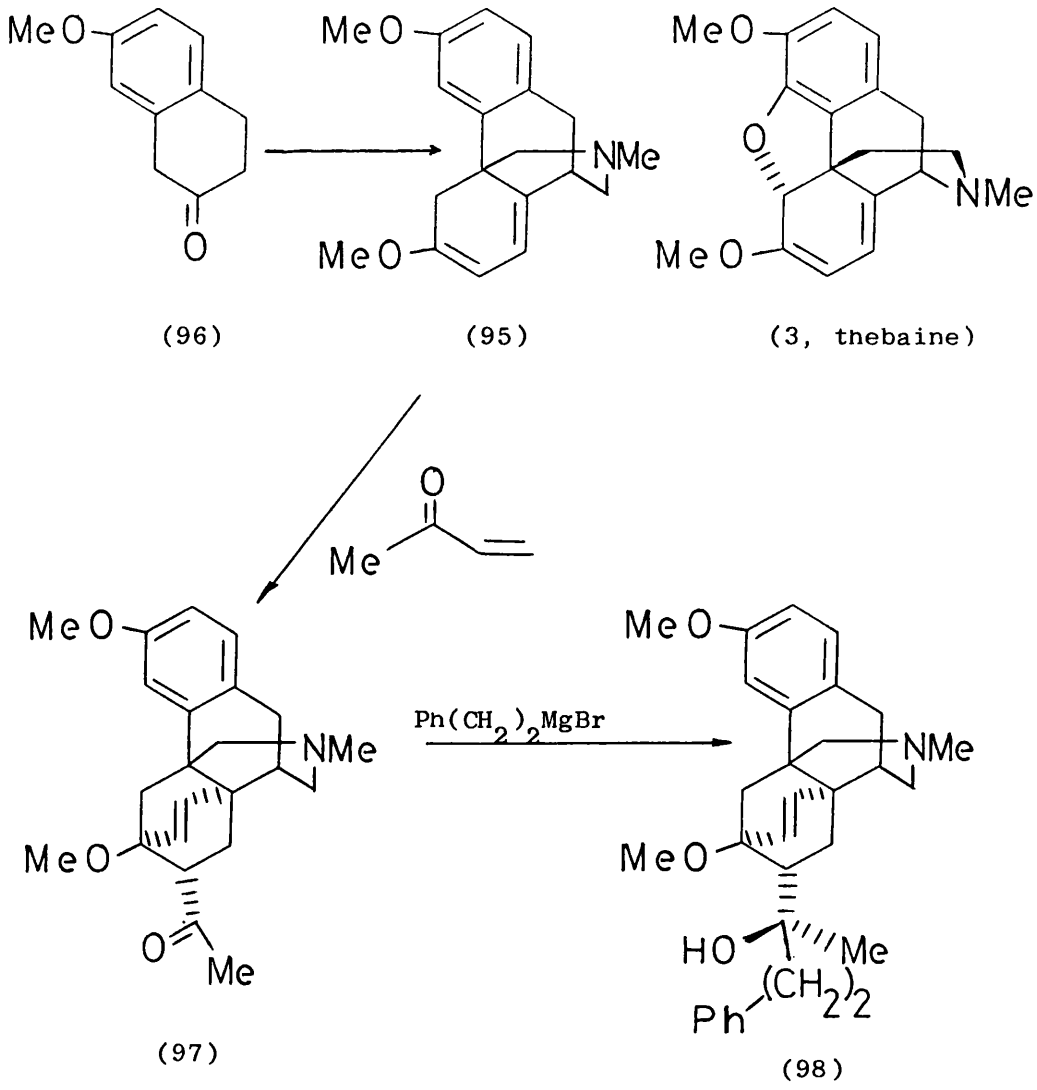
(87) (87) (89) (88)

The next report of synthetic studies on this ring system appeared in 1965[93], and in this report a synthesis of the unsubstituted 4a,10-(methaniminomethano)phenanthrene (90) was described. The starting point of the synthetic route was the ester-nitrile (91), which was de-esterified by ethanolic potassium hydroxide, and decarboxylated by concentrated hydrochloric acid to form the nitrile (92). The cyano group was selectively reduced by lithium aluminium hydride and aluminium chloride to give the amine (93). When the amine (93) was treated with formaldehyde in formic acid and then heated the 4-benzyloctahydro-isoquinoline (94) was formed. The formation of the desired ring system was effected by hydrobromic acid treatment yielding the cyclic amine (90).

In 1971 Wiesner[94] published a paper on the synthesis of the 4a,10-methanoiminomethano "analogue" (95) of thebaine (3). This synthesis comprised a multistage process starting from 7-methoxytetralone (96). Most of the steps involved are conventional, but it is interesting to note in view of our work which follows in the next section that Wiesner[94] proceeded to react the product diene (95) with methyl vinyl ketone to form the "Bentley adduct" (97)[64] which was further reacted with phenethyl magnesium bromide producing in turn the tertiary carbinol (98).


EtOOC
CN
(1) KOH
(2) HCl
CN
LiAlH4
AlCl3
NH2
(1) HCOOH
HCHO
(2) 130°C
NH
HBr
N
H

(91) (92) (93) (94) (90)

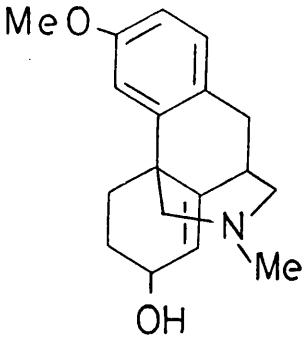


(96) (95) (3, thebaine)

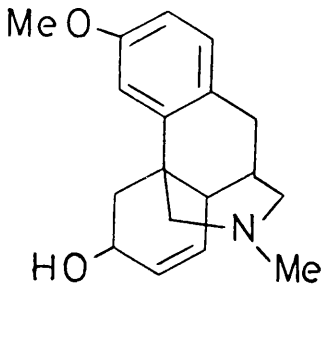
(97)

(98)

In connection with this work two patents [95,96] were published in which compounds of the type (98), (99) and (100) were claimed to have analgetic and antimicrobial activity.



(99)



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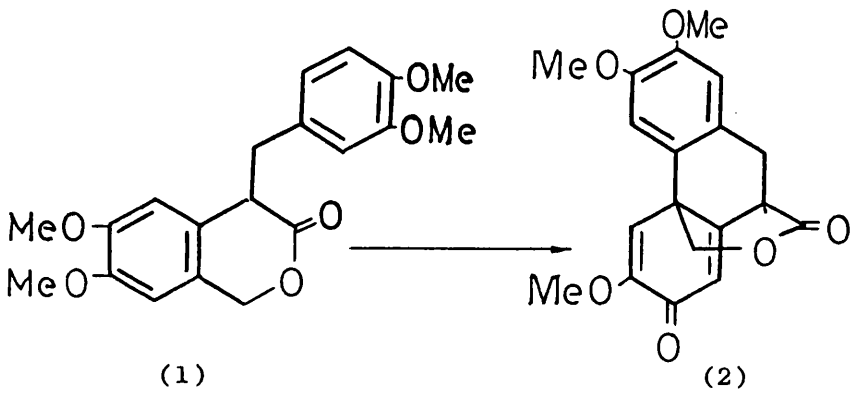
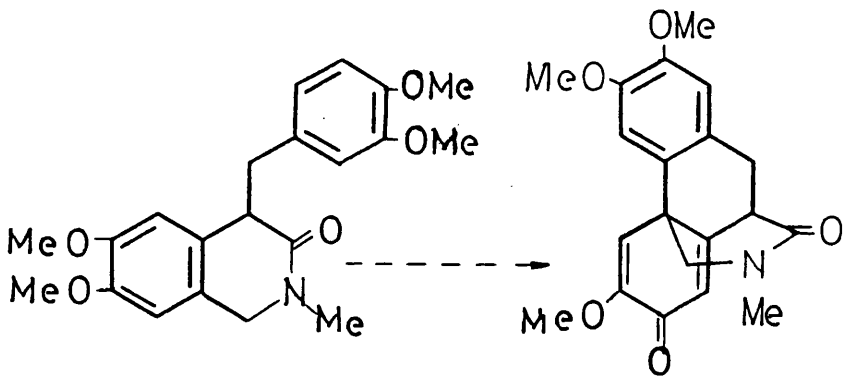
DISCUSSION

The report[1], in 1972, by Sainsbury and Schinazi that the isochroman-3-one (1) could be oxidised at a platinum anode to give the 4a,10-(methanoxymethano)phenanthrene[2] (2), prompted an interest in the related lactam[3,4,5] (3). If this compound (3) were to behave in a similar manner it would produce the aza analogue (4) and this result would then be of value since it constitutes a direct entry into the 4a,10-(methaniminomethano)phenanthrene ring system (see introduction p. 30).



(1) (2)

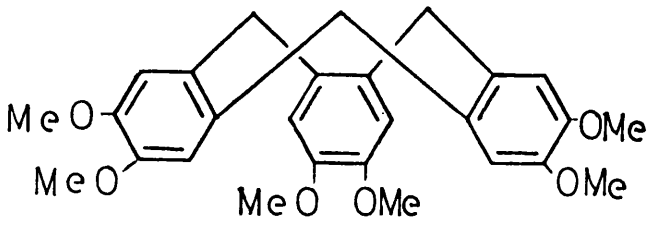


(3) (4)

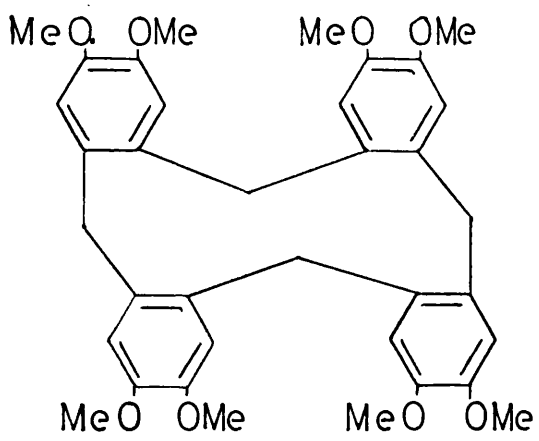
With this aim work was undertaken to provide a viable synthesis of the lactam (3) since previous attempts had been unsuccessful[3,4,5]. In assessing the various approaches to this compound the obvious disconnection is the bond between the 4 position of the 1,4-dihydro-3(2H)isoquinolone[8] (5) and the dimethoxybenzyl substituent (6).

(5) (6, X = leaving group).

Wyatt[4], and Carmody[3] showed that alkylation of the anion generated from (5) could be achieved with simple alkyl halides, such as ethyl bromide, but unfortunately the use of dimethoxybenzyl halides (6, X = Cl or Br) is precluded, since these substrates react with themselves in the presence of bases to form the so-called tri- and tetra-cycloveratrylenes (7)[3,6] and (8)[3,7].



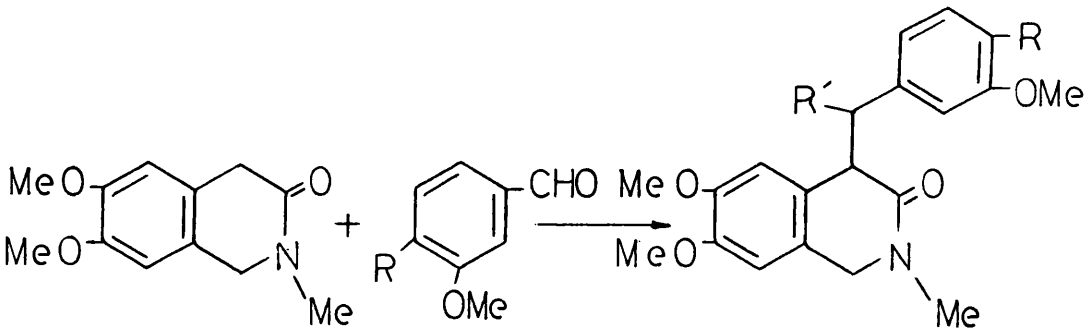
(7)



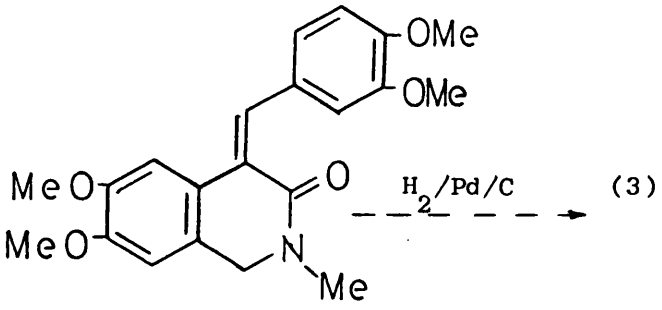
(8)

An alternative is to carry out either c-acylation or aldol type reactions upon the isoquinolone[8] (5) and we began this study by treating the lactam (5) with the hindered base potassium hexamethyl disilazide (KHMDS) and adding veratraldehyde (9). No alkylated products were detected (TLC), or isolated, but the starting materials were returned together with some intractible material.

Since this first attempt failed we considered that the initial aldol product (11) was unstable, undergoing a retro-aldol reaction on work-up and possibly some dehydration to the benzylidene derivative (12) which then reacted further. Should the latter course be followed then hydrogenation of the reaction mixture immediately prior to work-up would reduce the newly created double bond and provide some of the desired substrate (3). However, when this was attempted no such product was detected and starting materials were again returned.

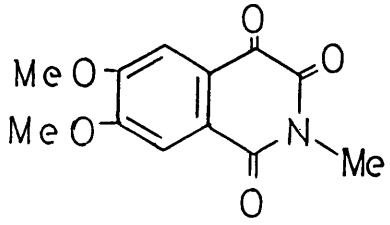


(5) (9, R = OMe) (13, R = H) (3, R = OMe, R' = H) (10, R = H, R' = OH) (11, R = OMe, R' = OH)



(12)

Carmody[3,5] had already carried out a few preliminary experiments in this area; he was able, for example, to isolate the aldol product (10) from the base catalysed reaction between the lactam (5) and 3-methoxybenzaldehyde (13), but he also failed to obtain a similar product with veratraldehyde (9). Carmody's compound (10) proved to be unstable breaking down on attempted recrystallisation, acid or base treatment to the trione (14).

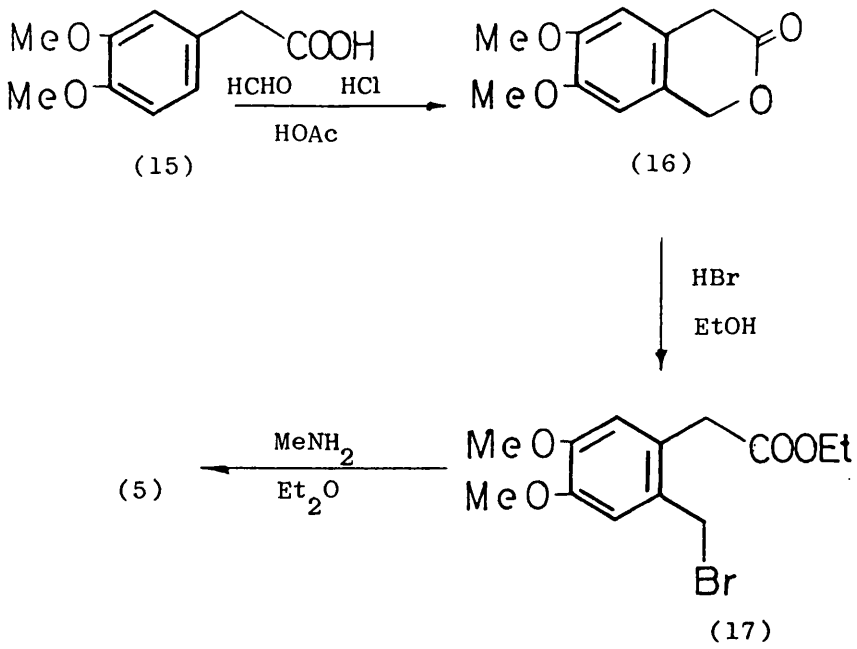


(14)

This may reflect a retro-aldol reaction returning the lactam (5) which then becomes oxidised in air to the trione (14) and it thus seems that our expectation of a facile dehydration within the aldol product is not justified. As mentioned above by leaving out the hydrogenation step we had hoped to obtain the appropriate aldol compound (11), just as Carmody[3,5] had done, but such a product was not isolated with veratraldehyde (9). Since nucleophilic additions to this aldehyde are common place it seems that retro-aldolisation occurs even more easily than in the case of the monomethoxyl analogue, although it is not obvious why this should be.

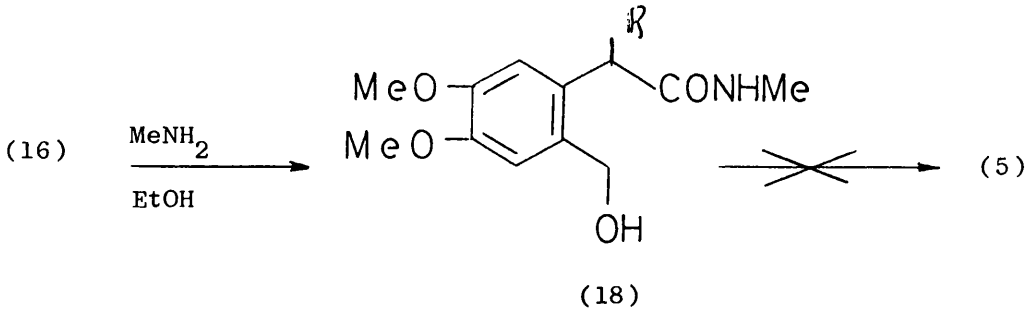
We varied the conditions of the reaction using other bases and solvent systems and even switched to condensation attempts in acidic media[11] but all to no avail.

At this point it is worth noting that isoquinolone (5) required for the previous experiments was obtained by the method of Brossi[8] with improvements by Wyatt[4]. For this preparation the starting material was the acid (15) which was reacted with formalin and hydrochloric acid in glacial acetic acid to yield the isochroman-3-one[10] (16) in 66% yield. Lactone ring opening with dry ethanol and hydrogen bromide formed the unstable bromo-ester (17), which was ring closed with methylamine in dry ether giving the lactam (5).



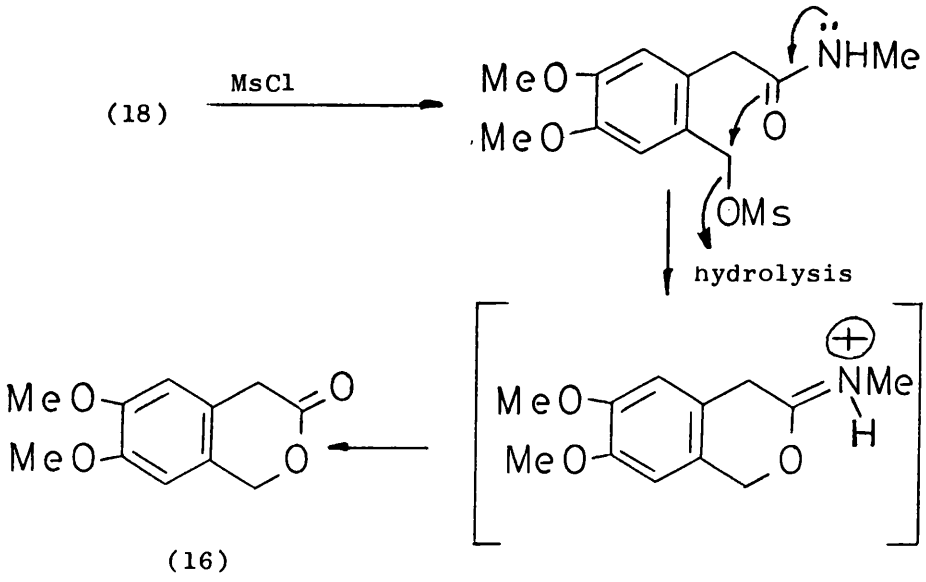
This route is not applicable to large scale reactions and we concluded that if the alkylation studies had proved successful large quantities of the lactam (5) would be needed and in parallel with the experiments just described we set about designing a more practicable synthesis of this compound.

One approach which we considered as a potential source of large amounts of the lactam (5) was the modification of the lactone (16), firstly by ring opening with methylamine to the amido-alcohol (18) and then ring closure.



(18)

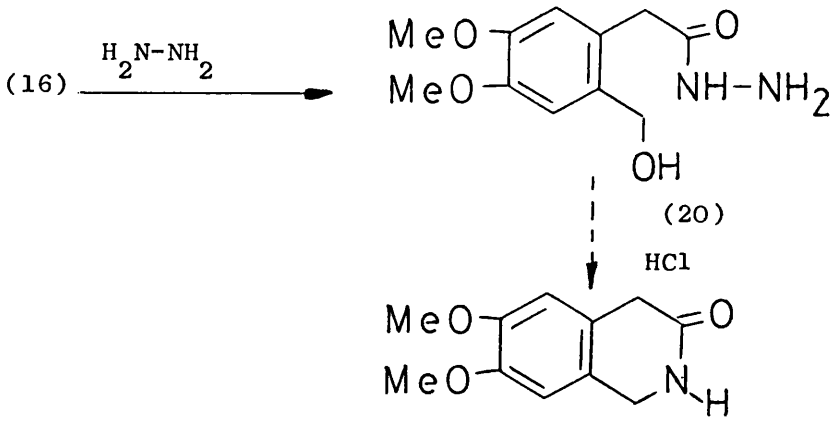
However, attempts to achieve the last step using methane sulphonyl chloride (MsCl)/pyridine (py)/triethylamine or diethylazodicarboxylate (DEAD)/triphenylphosphine (Ph_3P)[12] failed. In the first case, the lactone (16) was returned suggesting that the oxygen atom of the amide unit has more nucleophilic character than that of the nitrogen lone pair under these conditions.



(16)

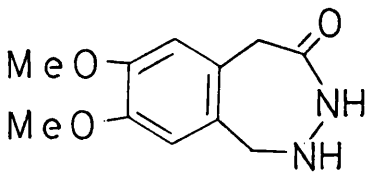
The DEAD/Ph_3P case formed a complex mixture which caused us to view an alternative approach to the desired lactam (5).

We then turned our attention to the reported synthesis, by Rosen and Popp[13], of lactam (19). The isochromanone (16) was reacted with ethanolic hydrazine to form the hydroxyhydrazide (20). Dilute acid treatment of (20) yielded a colourless crystalline compound identical in properties with that claimed by Rosen and Popp[13] for compound (19).



(19)

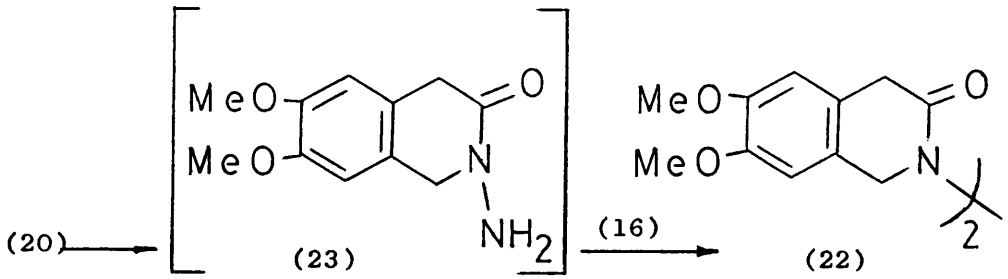
However, we were at a loss to understand how this product might form since the terminal NH_2 unit of the hydrazinyl function would appear to contain the more basic nitrogen atom. This would suggest a more likely product should be the diazapeinone (21). Such a structure was dismissed by Rosen and Popp from a consideration of analytical data.



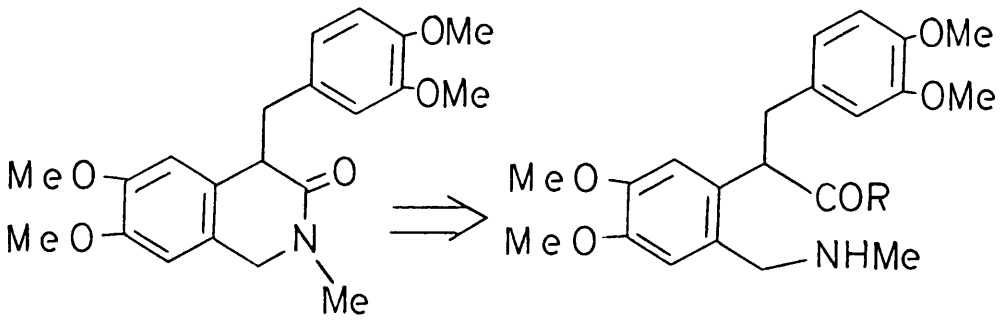
(21)

We were also puzzled by the absence of an NH absorption band in the infrared spectrum, however, examination of the mass spectrum showed a molecular ion peak at 412. This

information points to a dimeric product of the form of the dilactam (22) which is formed from hydrazide (20) by nucleophilic displacement of the benzylic alcohol moiety to form the intermediate (23). Another product from this reaction is lactone (16)[13] which is formed from (20) by the competing nucleophilic displacement of the oxygen atom of the amide function. The product dilactam (22) is thus formed by the intermediate aminolactam (23) reacting with the lactone (16).



The failure of C-4 alkylation of 1,4-dihydro-3(2H)isoquinolone (5) with benzylic substrates prompted a reinvestigation of the retro synthetic analysis of the desired 4-benzyl-isoquinolone (3). This compound should be available from the amino-acid (24) or the amino-ester (25) using well established procedures.

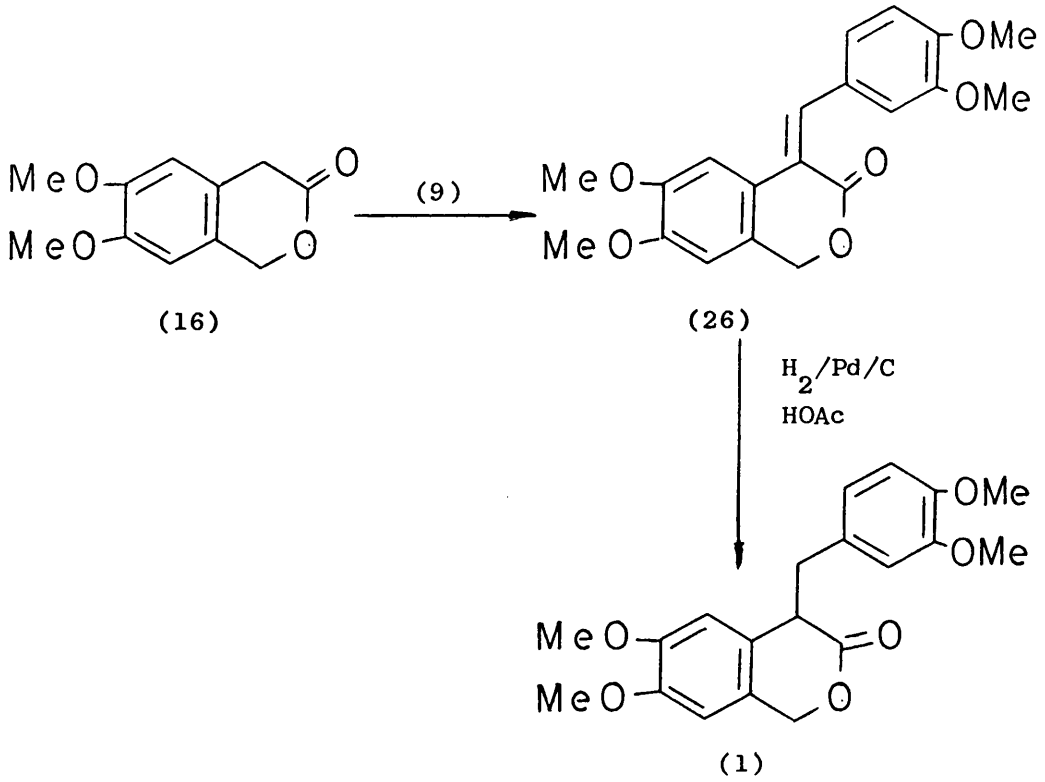


(3)

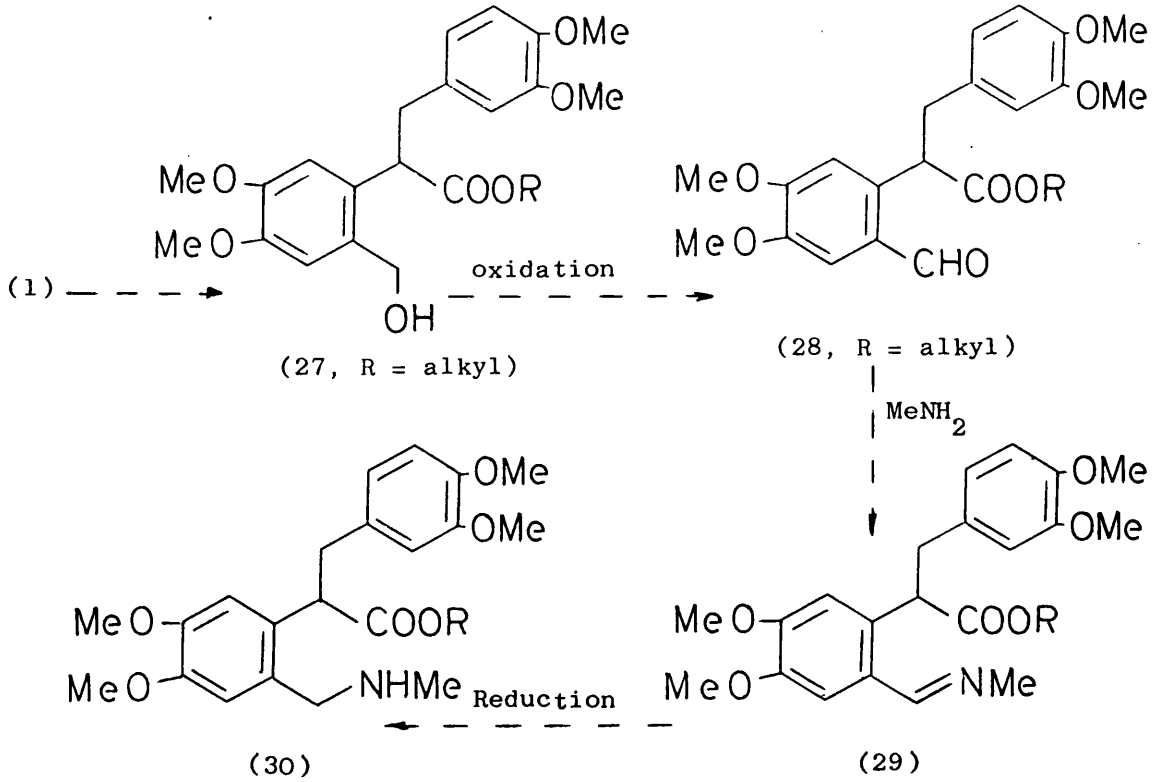
(24 R = OH)

(25 R = OMe)

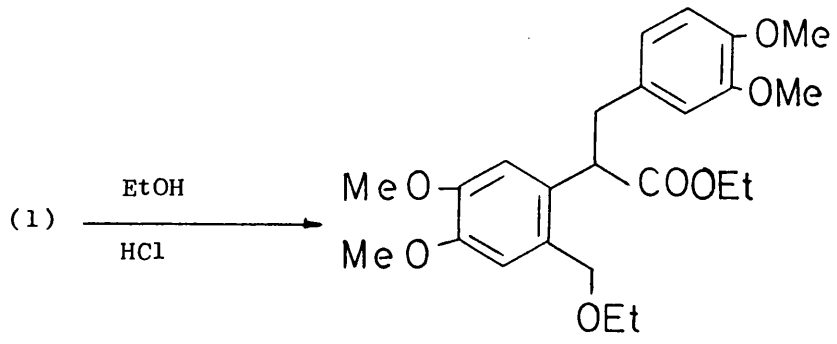
The proposed route to compounds (24) and (25) was from the lactone (16) which was functionalized at C-4 by treatment with piperidine and veratraldehyde (9) to the benzylidene (26)[2] in 60%. Reduction with Adam's catalyst in glacial acetic acid[2] gave variable results (long reaction times and poor yields) but changing the catalyst to 10% palladium on charcoal gave an almost quantitative yield of the 4-benzyl isochromanone (1).



The introduction of the nitrogen bearing unit was envisaged via the following strategy; lactone ring opening of the substrate (1) to the hydroxy ester (27), followed by oxidation to the aldehyde (28), then reaction with methylamine to form the imine (29). This imine (29) could then be reduced to the desired amino ester (30).



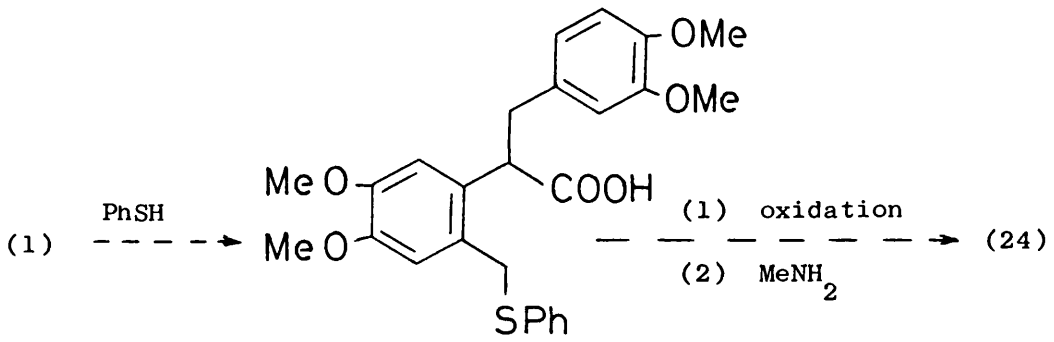
However, lactone ring opening experiments with the substrate (1) and t-butanol/sulphuric acid, isobutene/sulphuric acid, sodium methoxide/methanol, and methanol/potassium carbonate[14] all failed to produce a hydroxy ester (27). It is interesting to note that treatment of the lactone (1) with ethanol/hydrochloric acid produced the ether-ester (31).



(31)

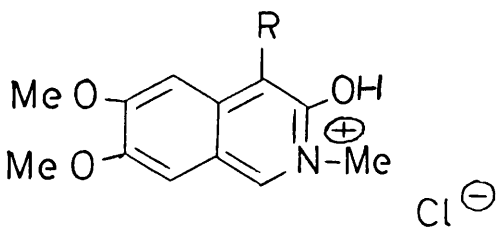
The failure of the above experiments is presumably due to the nucleophilicity of the alcohol moiety in the hydroxy esters (27), which on formation displaces the alkoxy group reverting to the starting material (1) a phenomenom which is not uncommon[15].

As the hydroxy ester (27) were unavailable by this method an alternative approach was sought, one such is the production of a ω-arylthiocarboxylic acid (32) from the lactone (1) using benzenethiol and a Lewis acid[16]. Oxidation of the thio ether (32) followed by nucleophilic displacement with methyl amine (or equivalent nitrogen nucleophile) should then yield the amino acid (24).



(32)

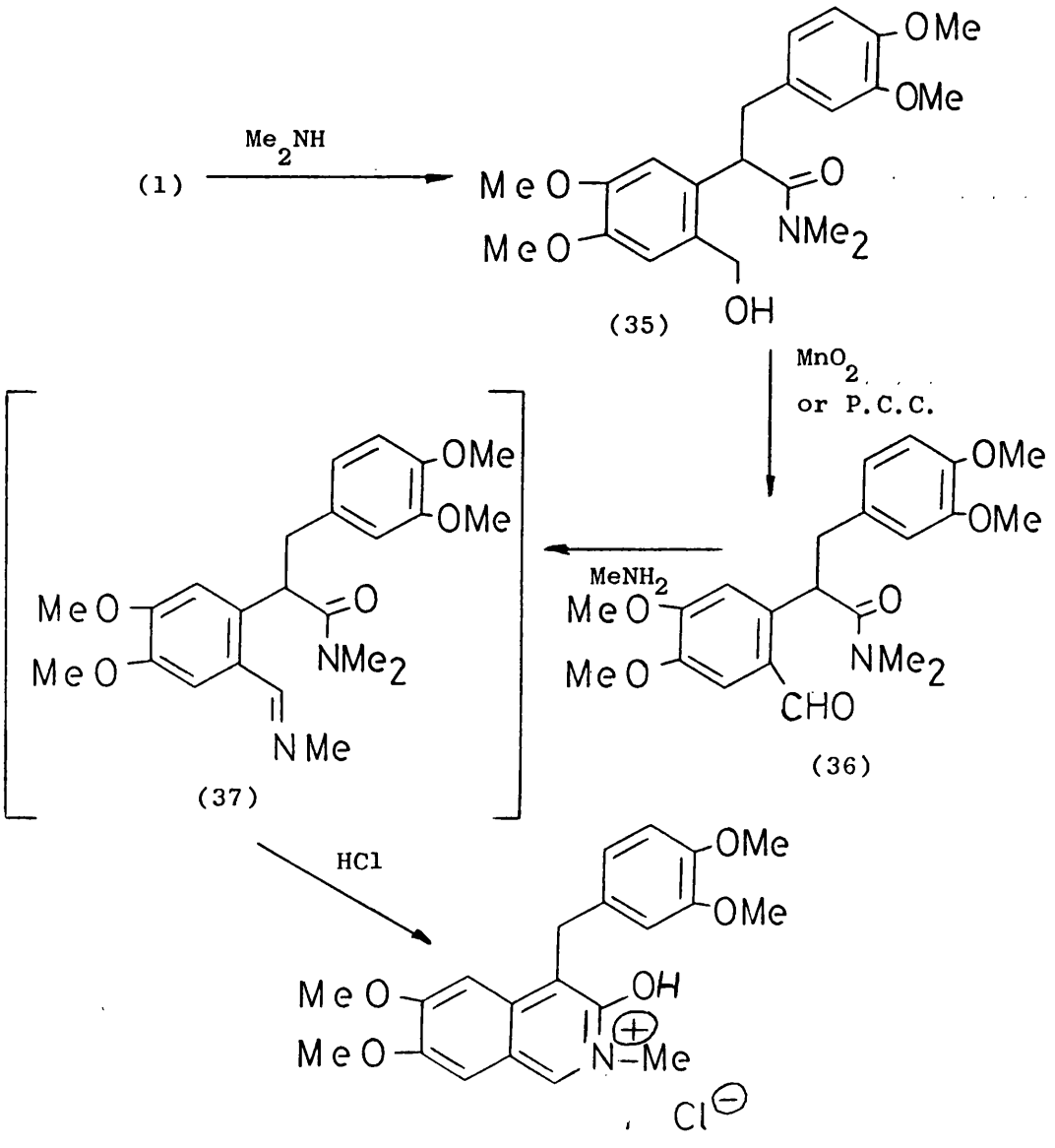
Before this work could be implemented, however, the author's attention was redirected to the work of McCorkindale and McCulloch[17] who synthesised the isoquinolinium chloride (33).



(33 R = H)

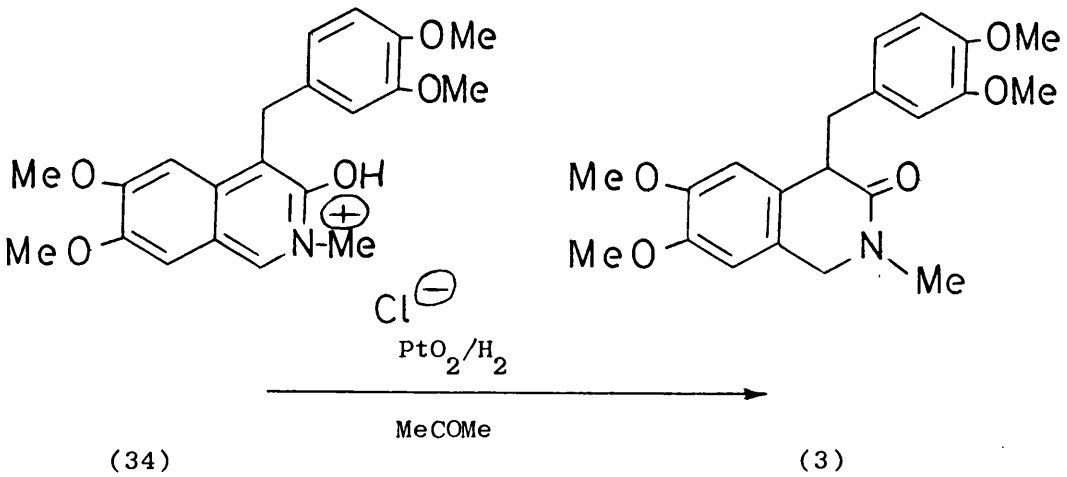
(34 R = 3,4-$(MeO)_2C_6H_3CH_2$.)

Carmody[3] repeated this synthesis and prepared the corresponding 4-(3,4-dimethoxybenzyl)analogue (34) using the following pathway. Lactone (1) was reacted with dimethylamine in ethanol to give the amido alcohol (35), which was oxidised either with manganese dioxide in chloroform[18] or using pyridinium chlorchromate (PCC.) in dichloromethane[19] to give the aldehyde (36). Treatment of the aldehyde (36) with methylamine in ethanol, followed by the addition of hydrochloric acid gave the required salt (34) via the imine (37).



Carmody[3,5] was unable to reduce the salt (34) to the required lactam (3) using sodium borohydride, or palladium on charcoal, in both instances multi-component mixtures were obtained. He also found that the isoquinolinium chloride (34) was base and light sensitive and abandoned his work at this point.

We repeated this sequence of reactions and attempted reductions of the salt (34) in acid media using sodium cyanoborohydride in methanolic hydrochloric acid[20], unfortunately we also obtained a multi-component mixture. On the other hand hydrogenation of the salt (34) using Adams' catalyst in acetone produced the required lactam (3) as a colourless gum in 70% yield.

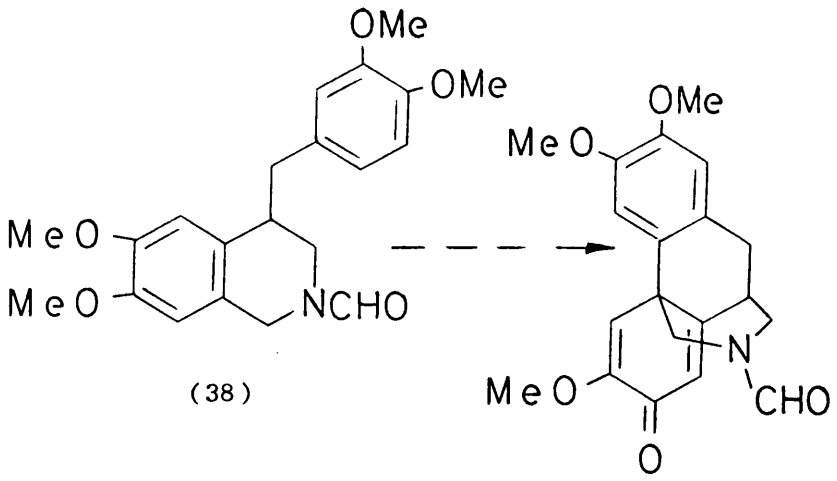


(34) (3)

The lactam (3) was then electrochemically oxidised at a carbon felt anode in dry acetonitrile solution containing sodium perchlorate as supporting electrolyte. The working electrode was maintained at a potential of 1.2v (vs. SCE.) and although the electrolysis appeared to consume the equivalent of 2F mol^{-1}, on workup only an intractable tar was obtained. As a varient a platinum gauze anode was used and the cell contents were maintained at a temperature of $0^{o}C$.

While these conditions were an improvement on the last experiment, as the electrolyte did not become as dark, the usual workup gave only a tarry material TLC analysis of which showed several components. We had noted that the lactam (3) is much less stable than the analogous lactone (1), tending to oxidise and discolour in air, so that although disappointed by this result, we were not surprised by it. That many products were produced by the anodic oxidation suggests intermolecular coupling to be preferred to intramolecular cyclisation, a common enough occurrence with nitrogenous substrates (see p. 60).

This failure caused us to consider N-acyl-tetrahydroisoquinolines as substrates for the reaction since there, at least in the 1-benzyl series are well known stable structures[21]. A suitable compound appeared to be the N-formyl derivative (38) which should afford the dienone (39) on oxidation.

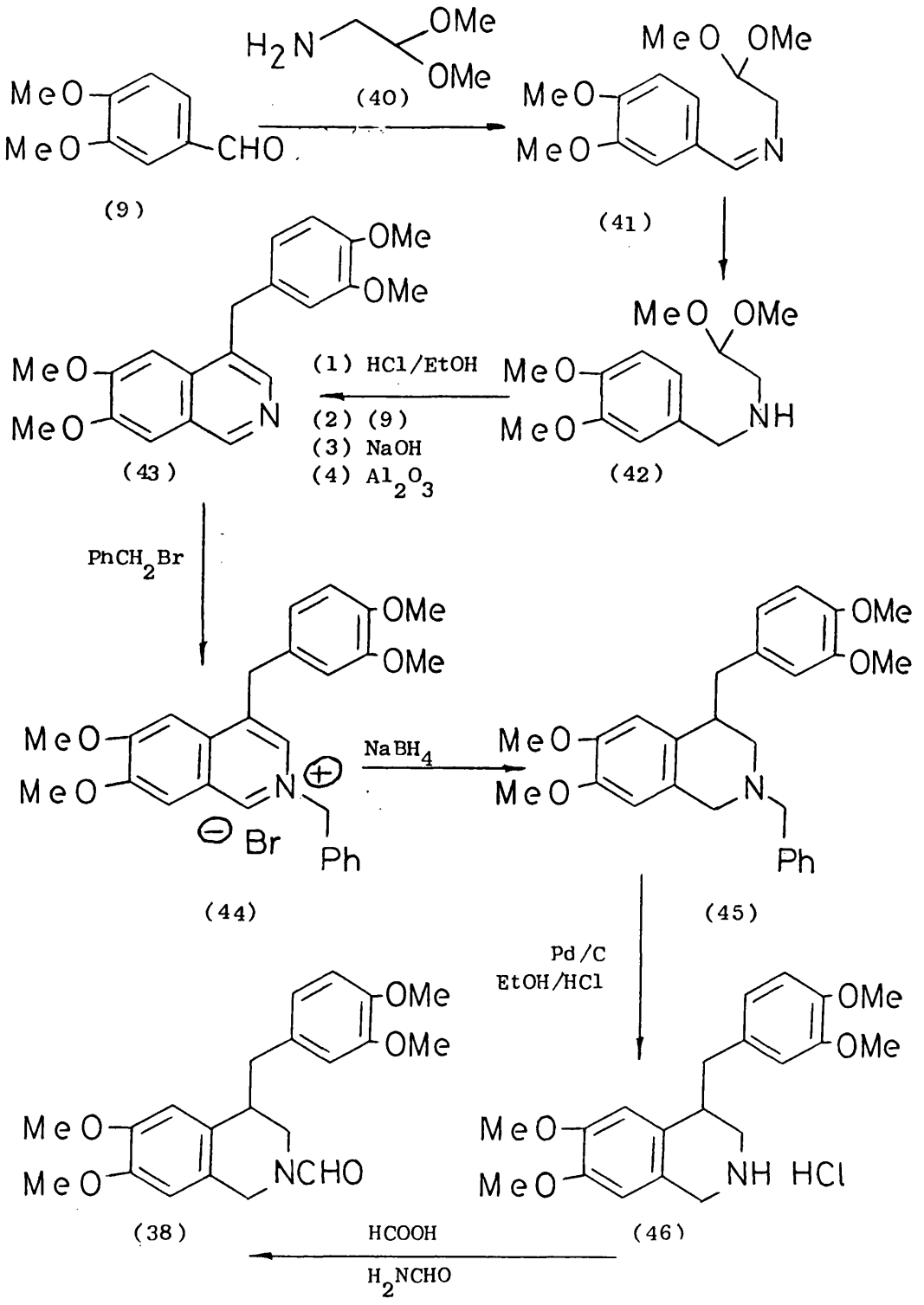


(38) (39)

The synthesis of the formyl conpound (38) was successfully completed in seven steps using the method of Warren[9] to prepare the parent isoquinoline (46). Veratraldehyde (9) was condensed with aminoacetaldehyde dimethyl acetal (40)to give the Schiffs base (41), this was reduced with sodium borohydride to form the secondary amine (42). The amine (42) was subjected to the conditions of the Bobbitt[22] variation of the Pomeranz-Fritsch[23-26] cyclisation to yield the required 4-benzylisoquinoline.

The A ring of isoquinolines is not readily reduced to the 1,2,3,4-tetrahydroisoquinolines under mild hydrogenation conditions[27]. Hence the isoquinoline (43) was quaternised using benzyl bromide in acetone to give the bromide (44). Sodium borohydride reduction of this product yielded the tetrahydroisoquinoline (45), which was N-debenzylated by hydrogen and 10% palladium on charcoal in the presence of

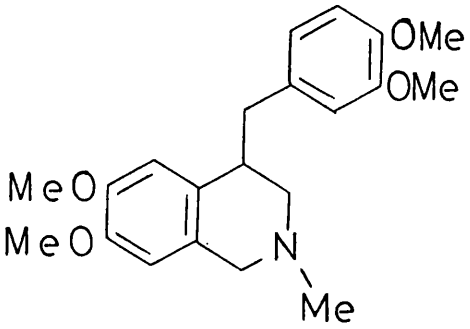
dilute hydrochloric acid to afford the hydrochloride salt (46). N-formylation was achieved using the method of Baxter[28]; the salt (46) was heated with formic acid and formamide to furnish the desired amide (38).



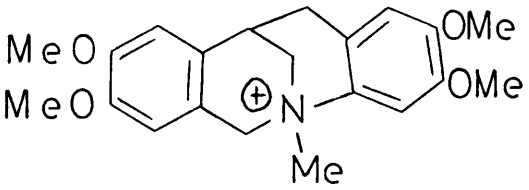
Electrochemical oxidation of the N-formylisoquinoline (38) at 1.22 V. (vs SCE) using a carbon felt electrode formed only polymeric tarry materials. This disappointing result is perhaps due to the conformation of the A ring of the isoquinoline, which is somewhat flattened by the N-formyl substituent causing restricted overlap of the two aryl units. The consequence of this situation is that on oxidation of the substrate intermolecular reactions occur in preference to the desired intramolecular ring closure, this process continues further forming polymeric products.

Previous workers had electrolysed the analogous N-methyl isoquinoline (47) which has an A ring which is held in a chair conformation, this allows the two aryl units to align to a greater extent than is possible in the N-formyl analogue (38).

Powell[29] oxidised the N-methyl isoquinoline (47) in neutral media and obtained the salt (48).

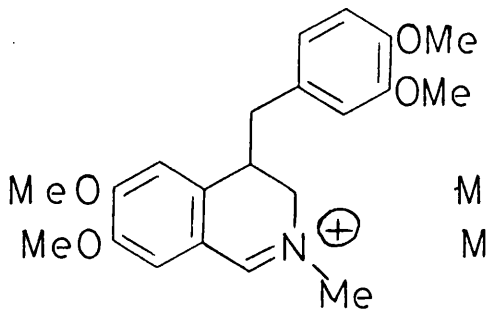


(47)

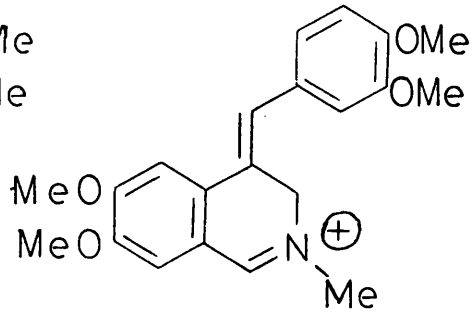


(48)

Carmody[3,5] showed that the hydrotrifluoroacetate salt of the amine (47) yielded the isoquinolinium salts (49) and (50) under similar oxidative conditions to those used by Powell.

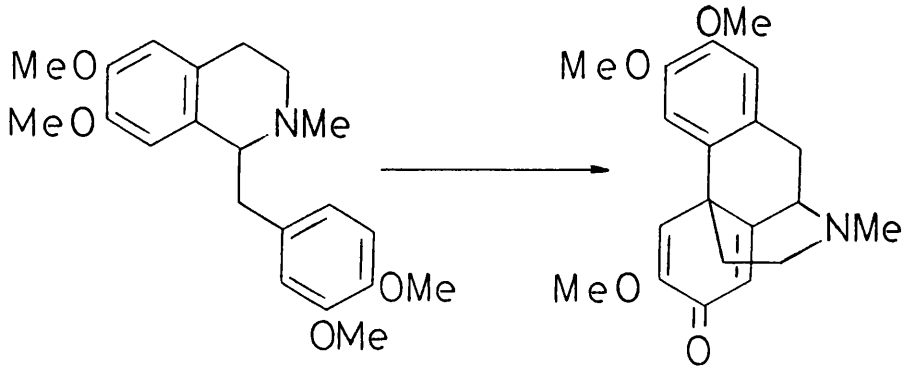


(49)



(50)

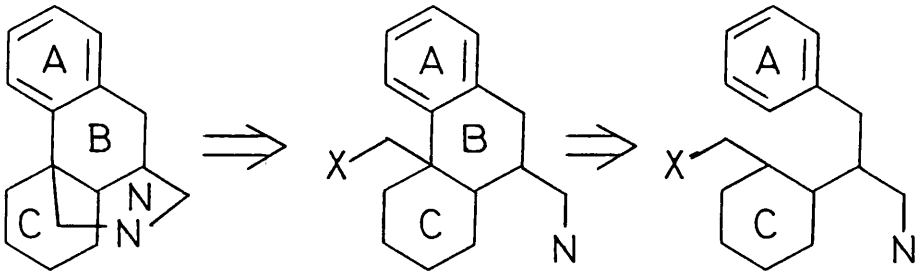
In the first case the salt (48) arises from a reaction between the oxidised 4-benzyl aryl ring and the nitrogen lone pair. In the second case the nitrogen lone pair is unavailable due to protonation and oxidation of the A ring occurs forming first the salt (49) and this is further oxidised to the salt (50). It is interesting that these products are formed in view of the results of Miller[30,31,32] who has shown that anodic oxidation of laudanosine (51) readily affords O-methylflavinantine (52).



(51) (52)

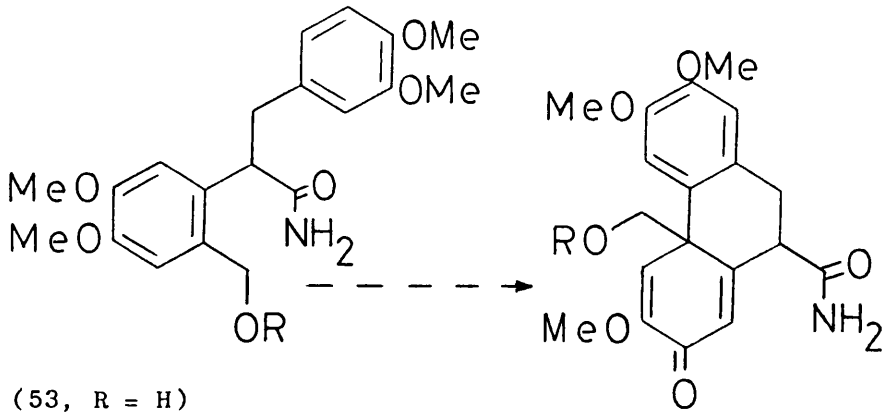
The factors influencing aryl-aryl coupling in preference to the other competing reactions is still under investigation by workers in this laboratory.

At this point we considered a novel approach to the desired 4a,10-(methaniminomethano)phenanthrene tetracyclic system (52a) (see introduction p. 30) in which the precursor has pre-formed A and C rings, cyclisation then forms the B ring and finally the N ring is constructed[33].



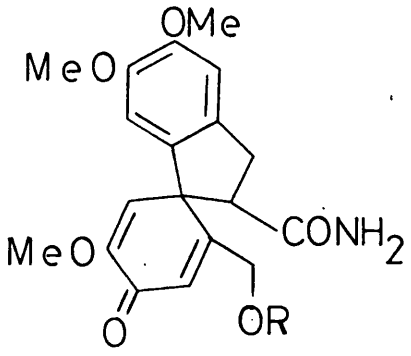
(52a)

The substrate we chose to test the feasibility of this route was the alcohol (53) this on oxidation could produce two aryl-aryl coupled products in which the methoxy substituents direct the coupling in a <u>para</u>-<u>para</u>' sense[34]. The two possible products being the dienones (55) and (56), of these the phenanthrene derivative (55) seemed the more likely.



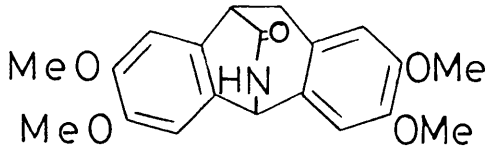
(53, R = H)
(54, R = Ac)

(55)



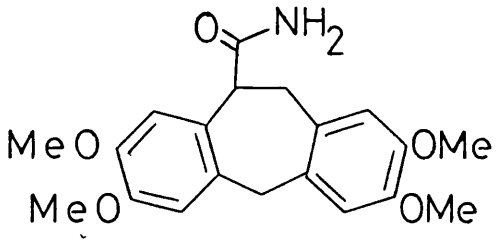
(56)

In either case, however, a dienone-phenol rearrangement[35] is a potential problem, i.e. the alkyl side chain γ - to the carbonyl group undergoes a 1,2-carbon-carbon bond shift allowing subsequent aromatisation of the dienone system. Should a hydroxymethyl unit be present this might even be lost as formaldehyde and for this reason and with the first limitation in mind we prepared the acetate (54). Treatment of the acetate (54) with vanadium trifluoride oxide (VOF_3) surprisingly produced the lactam (57) and the amide (58).



(57)

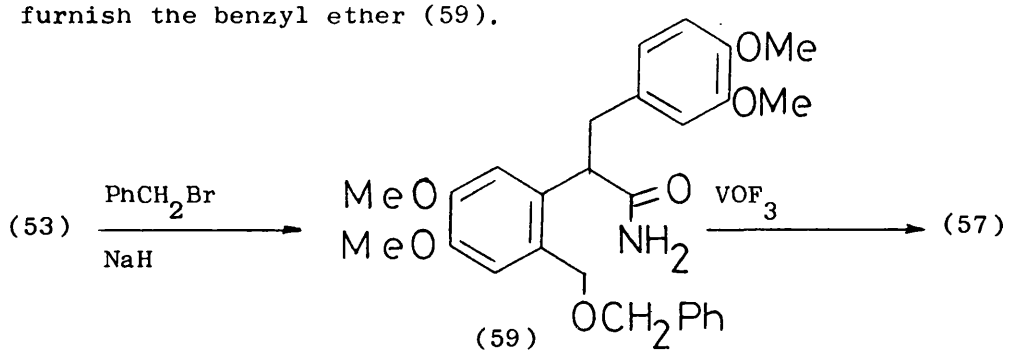
(54) $\xrightarrow{VOF_3}$



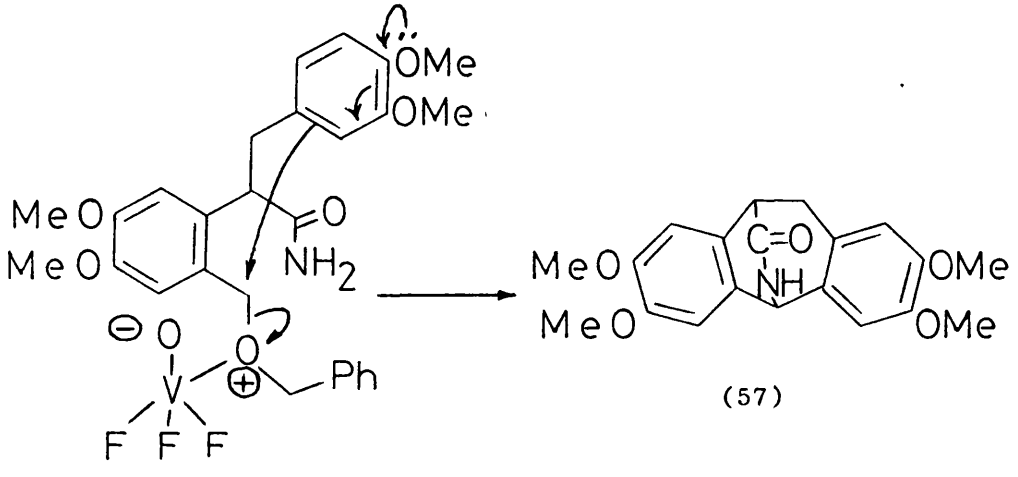
(58)

The lactam (57) is the first example of this ring system and it is presumably formed from the amide (58) by further oxidation at the doubly benzylic position, followed by intramolecular amide cyclisation. On the other hand the mechanism by which the acetate (54) affords the amide (58) is not so obvious, since the acetoxy group is required to leave with a pair of electrons. Due to the low yields of both products no attempt at proving the mechanism of lactam (57) formation from the amide (58) by oxidation of this substrate were undertaken at this point. To offset the formation of the

seven membered species we next employed the benzyl protecting group. Thus the amido-alcohol (53) was benzylated using benzyl bromide and sodium hydride in dimethoxyethane to furnish the benzyl ether (59).

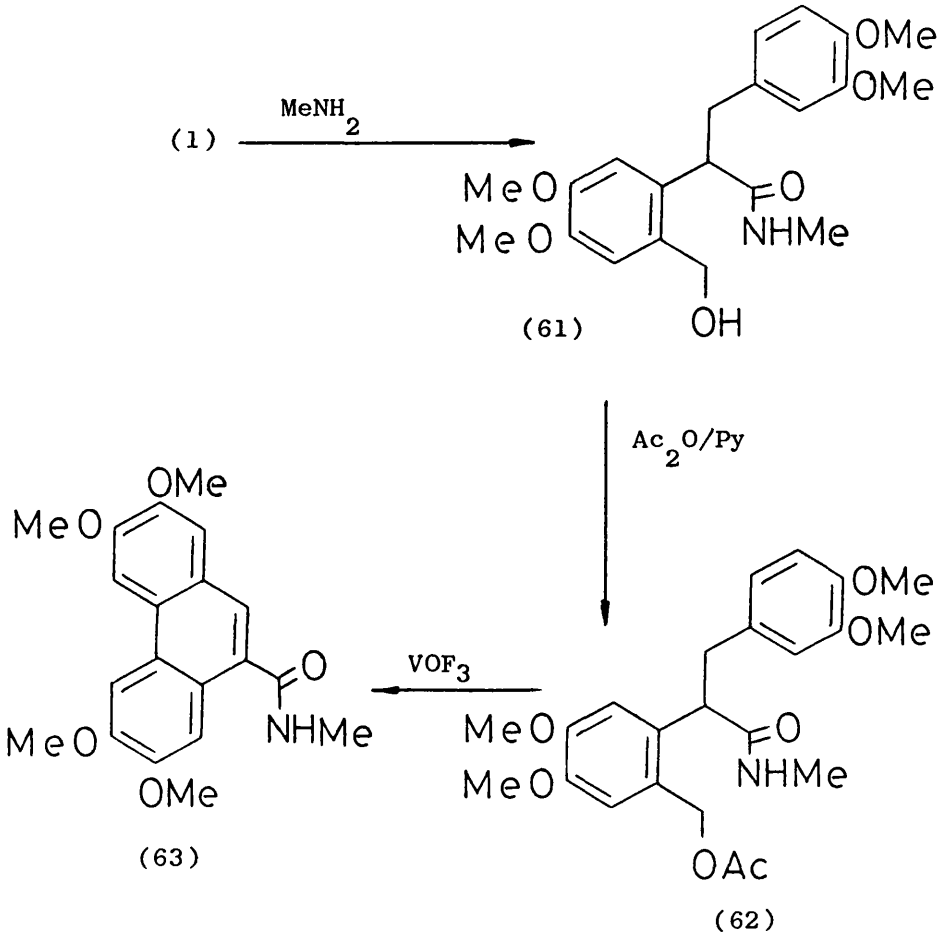


Oxidation of the benzyl ether (59) with vanadium trifluoride oxide (VOF_3) again yielded the lactam (57). This is also an unusual result, in that we considered the benzyloxy group to be less likely to fragment under the conditions of the reaction, yet a pathway for the formation of the lactam (57) must surely come about by the formation of a benzylic carbocation (or an equivalent species). Hence a possible mechanism is the formation of an ether-vanadium complex of the type (60) which facilitates a nucleophilic attack by the aryl moiety and hence the formation of the seven membered ring.



Presumably something similar occurs with the acetate (54).

In a parallel sequence of reactions the lactone (1) was ring opened with methylamine in ethanol to give the amido-alcohol (61)[3] which was acetylated with acetic annhydride and pyridine to form the acetate (62). Reaction of the acetate (62) with vanadium trifluoride oxide produced a small amount of a compound which has been assigned the structure (63).

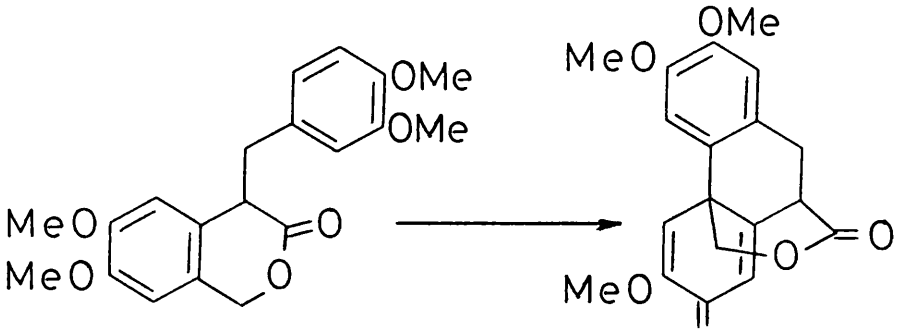


The structure of the phenanthrene (63) was assigned on the basis of spectral data, in particular the ultra-violet spectrum which was characteristic of a phenanthrene[36].

We cannot say why this reaction should differ from that observed with the previous acetoxy compound (54), but the yield

of isolated was very low and it is possible that the corresponding seven membered ring structure was "lost". In this case direct aryl-aryl coupling seems to have taken place with loss of the acetoxy methyl side chain at some stage.

The report by Sainsbury[1], that the spirodienone (2)[2] could be formed by electrochemical oxidation of the lactone(1), has been the key literature precedent for all the previous routes employed to form the desired 4a,10-(methaniminomethano) phenanthrene ring system (see introduction p. 30).

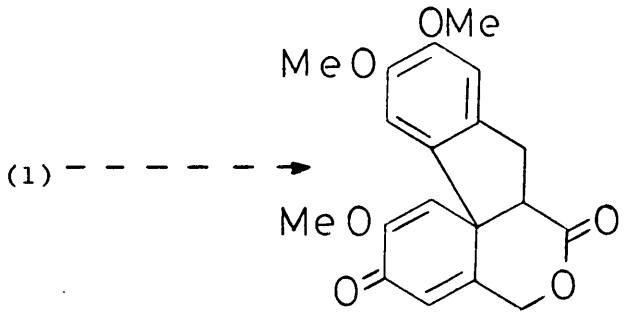


(1) (2)

The product (2) arises through direct coupling of the benzyl substituent with C_{8a} of the isochromanone ring followed by O-demethylation.

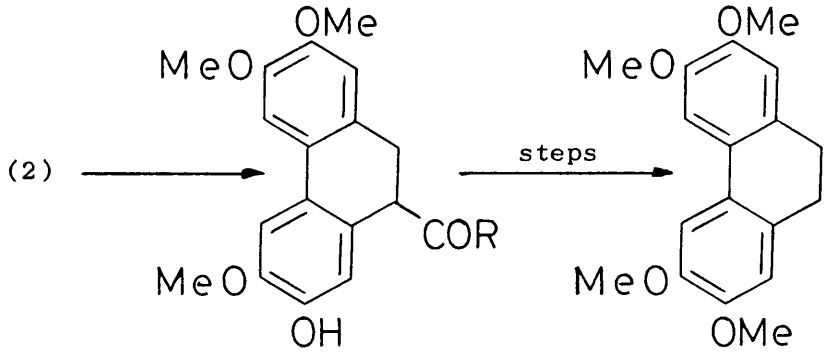
This has been the accepted normal coupling mode between aryl rings containing <u>para</u> directing substituents[34]. On further examination an alternative product could be formed from a <u>para</u>-<u>para</u>' coupling reaction of lactone (1), this being spirodienone (64), incidentally this product was dismissed by

Sainsbury[1] on the grounds of spectral data and the fact that a six membered assembly is usually more stable than the analogous five membered array.



(64)

Further indications that structure (2) was the product and not structure (64), came from reactions of the electrochemical product with ethanol/hydrochloric acid, methanol/hydrochloric acid and methylamine in ethanol[37]. These reagents caused lactone (2) to undergo a dienone-phenol rearrangement[35] with the concomitant loss of formaldehyde yielding the esters (65), (66) and the amide (67).

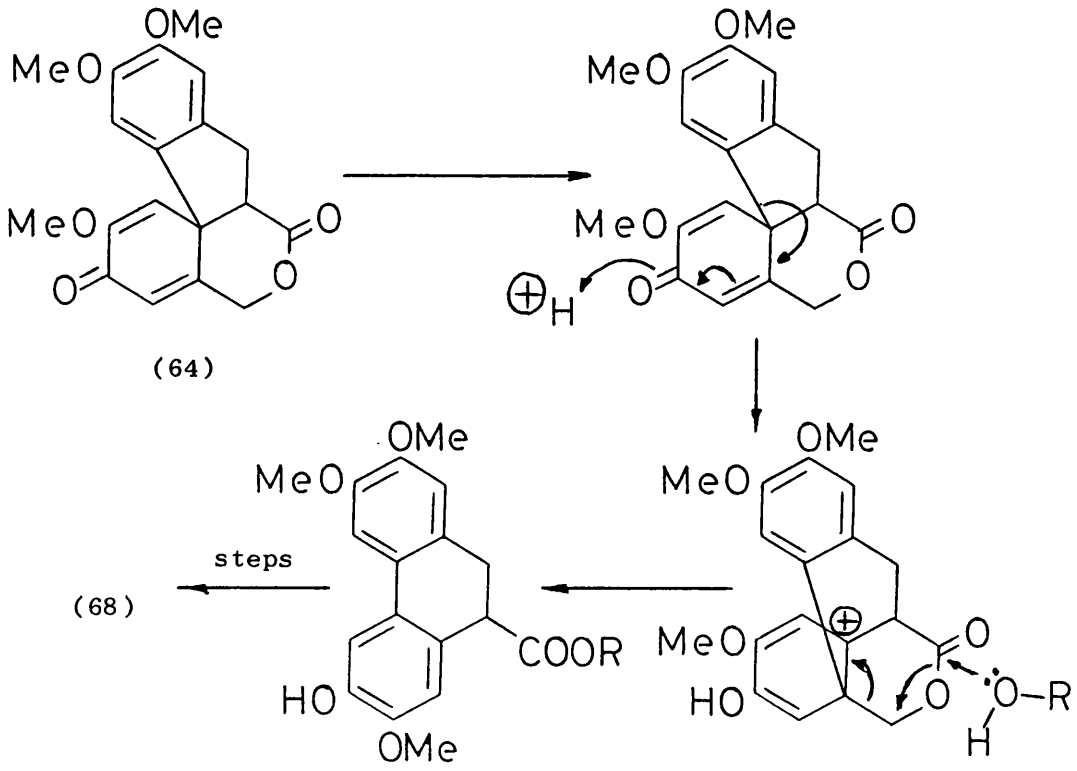


(65, R = OMe)
(66, R = OEt)
(67, R = NHMe)

(68)

The ester (66, R=OEt) was hydrolysed, decarboxylated and O-methylated to afford the known compound 2,3,6,7-tetramethoxy-9,10-dihydrophenanthrene (68) but at the time absolute structural confirmation of these degradation products was not achieved[38].

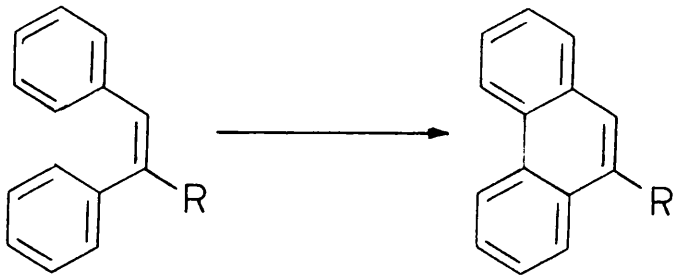
The five membered dienone (64) could also undergo a similar rearrangement to yield the phenanthrene-ester (69), which also could form the substituted dihydrophenanthrene (68) when subjected to the same degradative experiments as discussed above.



(69)

Before utilizing the dienone (2) as an intermediate in a synthesis of 4a,10-(methaniminomethano)phenanthrenes, we wanted to fully establish its structure by synthesising the phenanthrene-ester (65).

The projected route to the desired phenanthrene-ester (65) was based upon a stilbene (70) to phenanthrene (71) oxidative cyclisation, this has been accomplished by photochemical methods[38], by the use of inorganic oxidants[39,40,41] and by anodic oxidation[42].

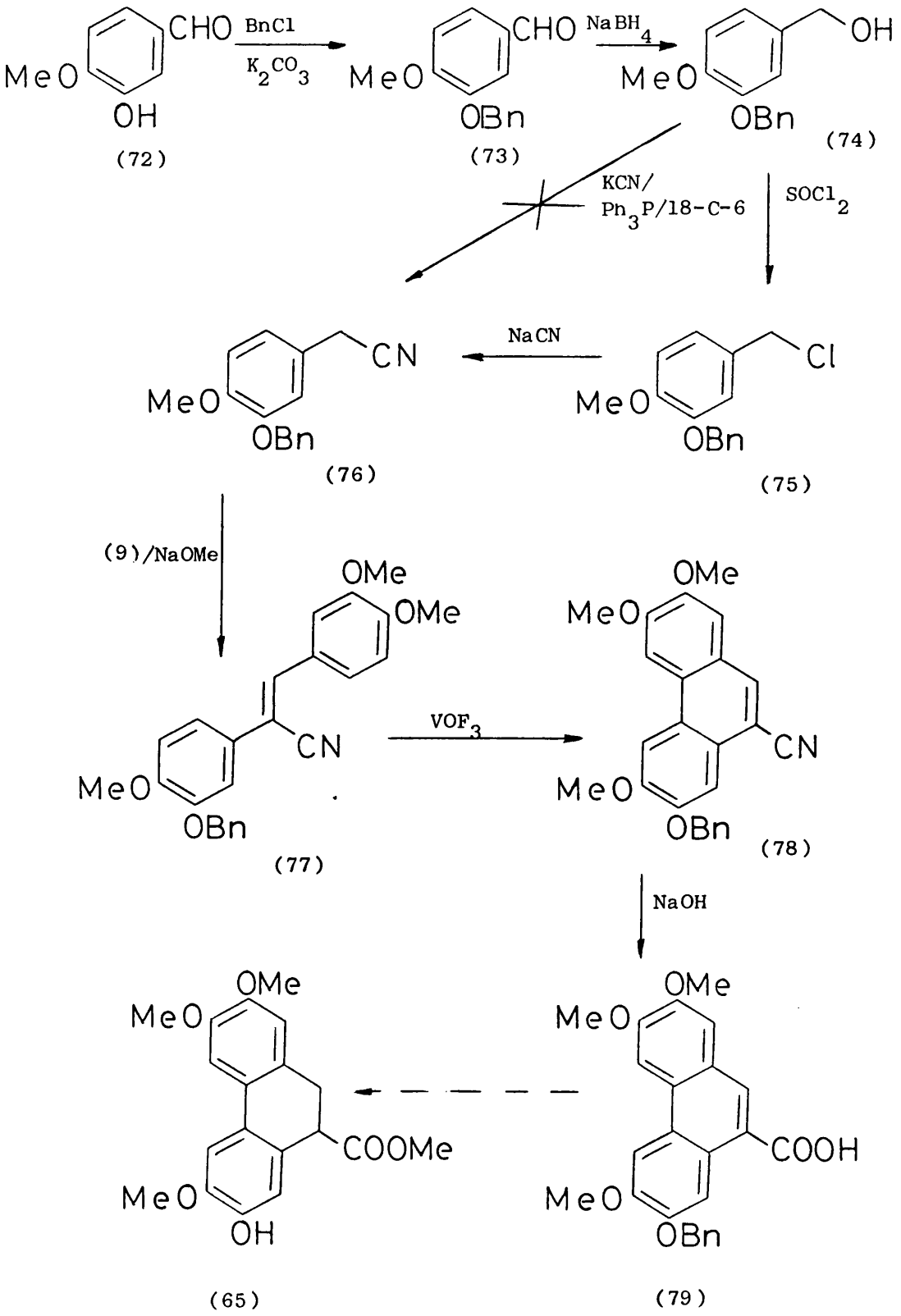


(70) (71)

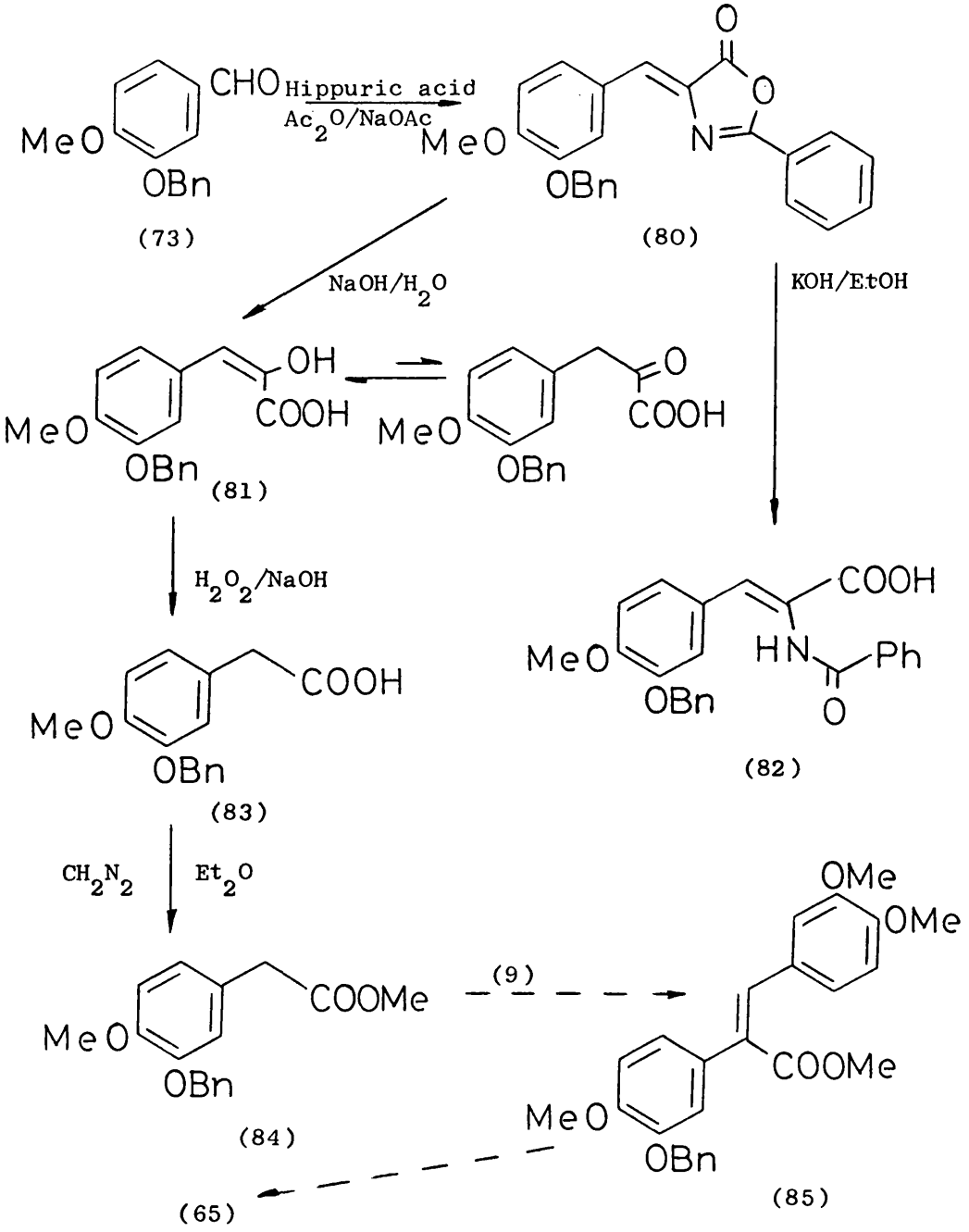
The starting point of the attempted synthesis of the phenanthrene (65) was from isovanillin (72) which was protected as the benzyl ether using benzylchloride, potassium carbonate in methanol to afford O-benzylisovanillin (73).[43,44] Reduction of the aldehyde (73) using sodiumborohydride in methanol gave the alcohol (74)[45], which was reacted with thionyl chloride in dry chloroform to form the chloride (75)[28]. The chloride (75) was then treated with sodium cyanide in dry dimethylformamide (DMF) to form the nitrile (76)[46,47]. Attempts at a direct conversion of the alcohol (74) to the nitrile (76) using triphenylphosphine, potassium cyanide, 18-crown-6 (Ph_3P, KCN, 18-C-6)[48] failed. This may be due to the use of triphenylphosphine instead of tributyl phosphine which was not available at the time. The latter is claimed to be far more effective as a reagent in this type of conversion[48].

The nitrile (76) was then converted to the stilbene (77) by a condensation reaction with veratraldehyde (9) using sodium methoxide in methanol as the base catalyst. Oxidative cyclisation of the stilbene (77) was effected by vanadium trifluoride oxide (VOF_3)[39] in dichloromethane/acetonitrile, producing the substituted phenanthrene (78). Hydrolysis of the nitrile moiety of phenanthrene (78) to the acid (79) using sodium hydroxide in various solvents produced a very low yield, this was due to the very low solubility of the nitrile in the solvents used. Many attempts at overcoming this problem were tried but without success.

This disappointing result caused us to view an alternative route to the phenanthrene-ester (65) based upon work by Robinson[44]. The protected aldehyde (73) was reacted with hippuric acid and sodium acetate in acetic anhydride to furnish the oxazolone (azlactone) (80). Base hydrolysis of the oxazolone (80) using sodium hydroxide solution yielded the pyruvic acid (81) which exists as the enol form. Mild base hydrolysis of (80) with potassium hydroxide in ethanol formed the glycine adduct (82). Decarboxylation of the acid (81) with hydrogen peroxide in sodium hydroxide afforded the acid (83)[49], which was then esterified with diazomethane to give the ester (84). Alkylation studies on the ester (84) were begun using veratraldehyde (9) and sodium methoxide but


CHO
BnCl
K_2CO_3
MeO
OH
(72)
OBn
(73)
$NaBH_4$
OH
(74)
KCN/
Pn_3P/18-C-6
$SOCl_2$
NaCN
CN
Cl
(76)
(75)
(9)/NaOMe
OMe
(77)
VOF_3
(78)
NaOH
COOMe
COOH
(65)
(79)

starting materials were returned with no detectable amounts of the stilbene (85). It appears that this alkylation requires stronger bases and strictly annhydrous reaction conditions.



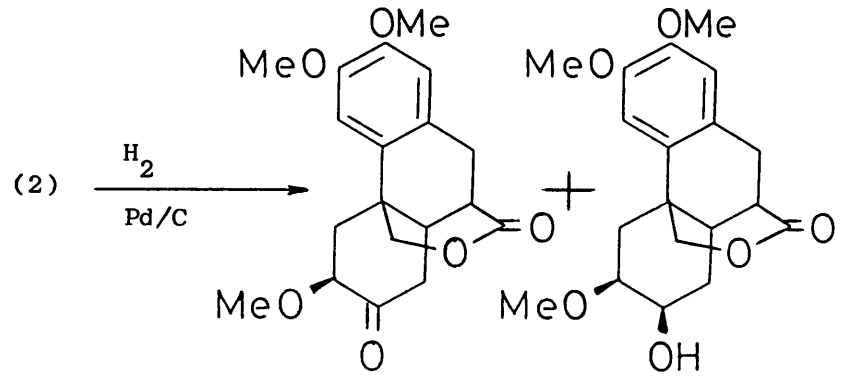
During the synthetic work aimed at the phenanthrene-ester (65) attempts at growing a suitable crystal of spirodienone (2) for x-ray analysis[50] were underway, unfortunately only fine amorphous solids were obtained. Nuclear Overhauser effect (n.O.e.) experiments were simultaneously carried out on the lactone (2) at Glaxo Group Research (Ware) and the results indicated that structure (2) was indeed correct.

This result caused us to terminate work on the synthesis of phenanthrene-ester (65), and now we started on the elaboration of the spirodienone (2), confident that we had the basic carbon skeleton necessary for the formation of the 4a,10-(methanimino methano)dihydrophenanthrene ring system.

Wyatt[2] claimed a 70% yield of spirodienone (2), from the isochromanone (1), but in similar experiments initial yields were in the range 10 — 28%. This disappointing series of results caused us to look carefully at the reaction conditions for the electrochemical generation of spirodienone (2). Our early experiments were carried out using a carbon felt anode and a mercury pool cathode at room temperature, with a substrate concentration of about 0.05 mol. dm^{-3} in acetonitrile solution. By doubling the substrate concentration dimeric products (86) (see p. 88) were formed as the major reaction products along with polymeric products.

A reduction of the substrate concentration down to about 0.025 $mol.dm^{-3}$, using a platinum gauze anode and a mercury pool cathode, at room temperature increased the yield of spirodienone (2) to about 30%. Running the electrolysis under the same conditions, but at a temperature of $0^{o}C$ to $2^{o}C$ increased the yield of spirodienone (2) to about 48%. This improved yield allowed us to prepare useful quantities of the product (0.5 g per electrolysis).

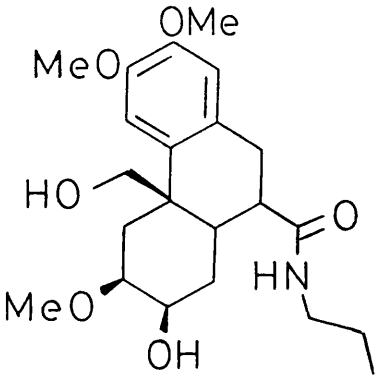
To offset possible later dienone-phenol rearrangements[35] we decided to hydrogenate the spirodienone (2) using 10% palladium on charcoal in acetone. Two products were formed and separated by column chromatography the minor product being the ketone (87) and the major product the alcohol (88)[51].



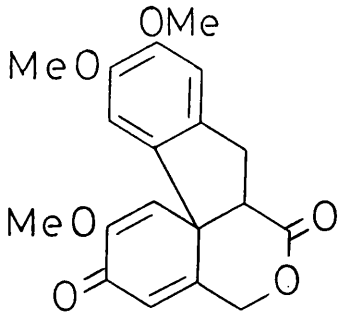
(87) (88)

The alcohol (88) was then used as the substrate for further elaboration, but reactions with methylamine in ethanol or n-propylamine in various solvents yielded only starting material. In order to increase the nucleophilic character of the amine we generated N-lithio-n-propylamine, using the method of Cannon[52] and reacted this species with the alcohol (88). This formed an

amide which we assigned the structure (89).



(89)

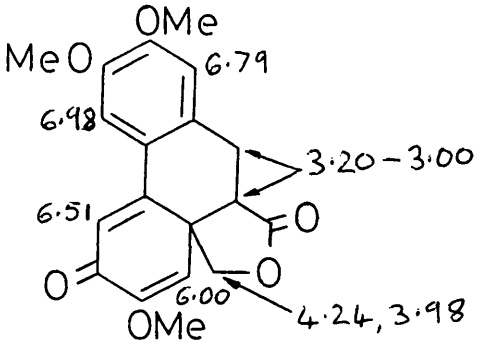


(64)

Analysis of the 250 MHz ^{1}H n.m.r. spectrum of amide (89) (see p. 129 for details) showed certain anomalies when applied to the assumed structure and this caused us to look closely at the n.m.r. spectra of the parent spirodienone (2), which was originally run at 60 MHz. Examination of the differential nuclear Overhauser effect (n.O.e.) spectra of the spirodienone (2) showed a 20 - 25% n.O.e. enhancement of the signal due to the proton at 6.51 δ when that of the aromatic proton at 6.98 δ was irradiated. Unless the proton assignments in the dienone ring are reversed this result rules out structure (2) and also the alternative (64) where the two protons in question are remote from one another.

That the proton assignments may not be interchanged is demonstrated by the fact that irradiation of the signal of the methoxyl protons at 3.76 δ causes a 12% enhancement of the single proton resonances at 6.00 δ and vice-versa. Irradiation at 6.00 δ also causes a 9% enhancement of one of the resonances

due to the methine proton α-to the lactone carbonyl group and a 4% intensification of the doublet (J = 12.5 Hz) at 4.24 δ which arises from the resonance of one of the protons of the oxymethano bridging unit, the other doublet of this AB system resonating at 3.98 δ is unaffected. These results establish the structure of the spirodienone as the five membered rearranged structure (90) and the ^{1}H n.m.r. assignments shown in formula (90) can now be made.

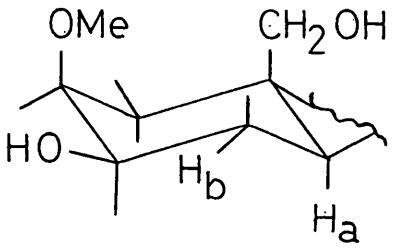


(90) (^{1}H n.m.r. data expressed in δ)

This structure is further evidenced by the i.r. lactone frequency of 1760 cm^{-1} which is more in keeping with a δ-lactone than for the previously assumed γ-lactone, originally this anomaly was put down to ring strain.

The amide product derived from the spirodienone (90) also gave a well defined ^{1}H n.m.r. spectrum at 250 MHz and after decoupling experiments it was possible to obtain all the coupling constants and proton-proton inter-relationships consistent with the new structure (91). It is apparent that ring A exists in

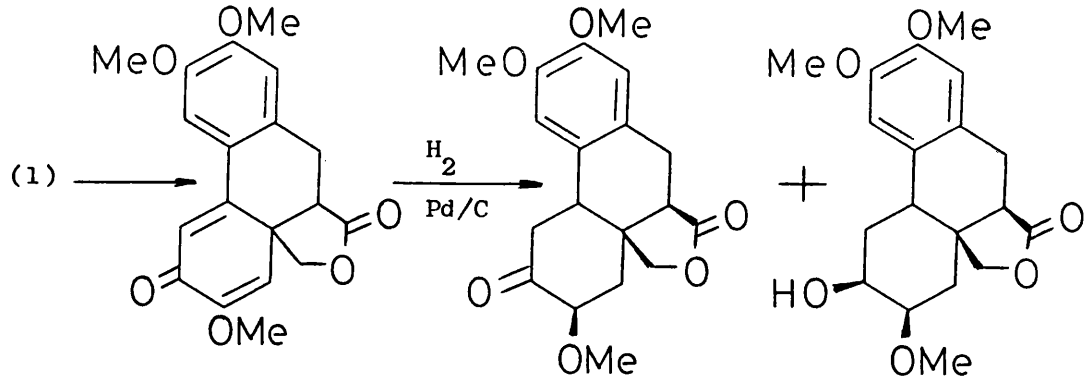
a chair conformation with an axial methoxy group and an equatorial hydroxyl group and that the structural fragment (92) is present. This fragment is present in both amides (89) and (91), the only difference is that proton Ha should display an extra vicinal coupling to H1O in amide (89). The dihedral angle is approximately 60^{o} so ^{3}J should be $\sim$ 3Hz. No such coupling is observed.



(92)

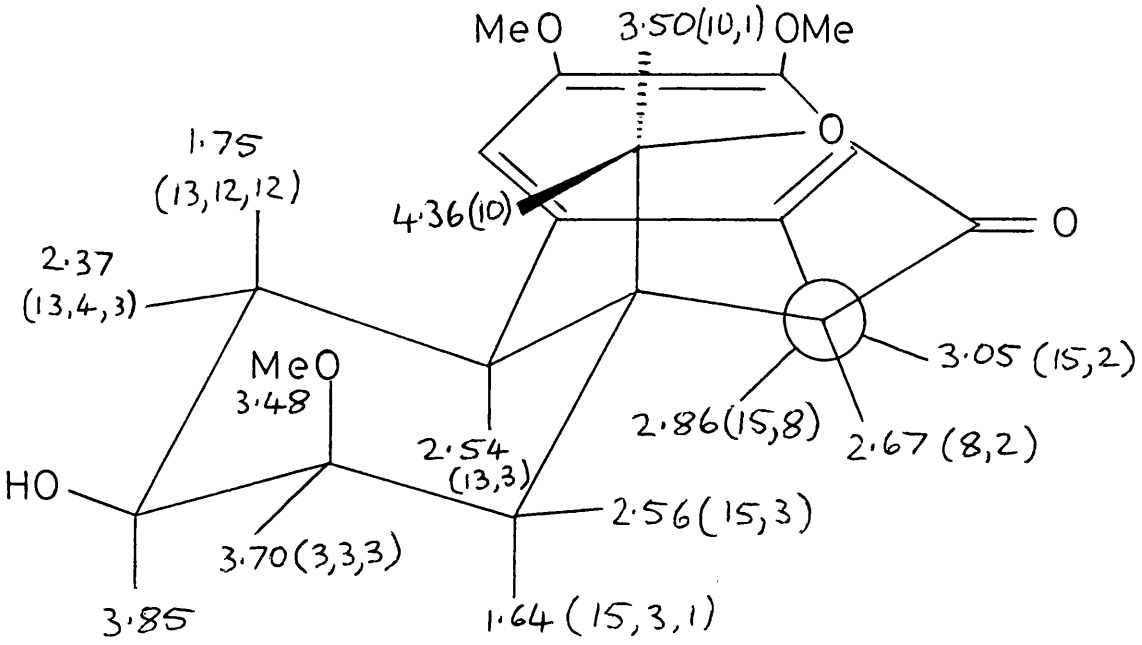
Apart from this one discordant note, the remainder of the spectrum could equally fit amides (89) or (91). However, saturation of the aromatic proton signal at 6.66 δ gives a strong n.O.e. for the resonance of Hb (see fragment (92)). This proton is conclusively identified because it is the only proton in the molecule with one large coupling (J gem)and 2 small ones (J eq/ax). Using models to compare the amides (89) and (91) shows that such an n.O.e. is impossible for the amide (89) since the two protons are much too far apart, whereas they are very close in (91) being some 2$\mathring{A}$ apart.

With this new data the whole series of compounds derived from the lactone (1) can now be reassigned, thus the electrochemical product the spirodienone (90) gave two products on hydrogenation the ketone (93) and the alcohol (94)[51]. The alcohol (94) afforded the amide (91) on treatment with N-lithio-n-propylamine[52].



On re-examination of the 250 MHz ^{1}H n.m.r. spectrum of the alcohol (94), a long range coupling ^{4}J = 1Hz is apparent between the 1-H axial proton and one of the 13-H methylene

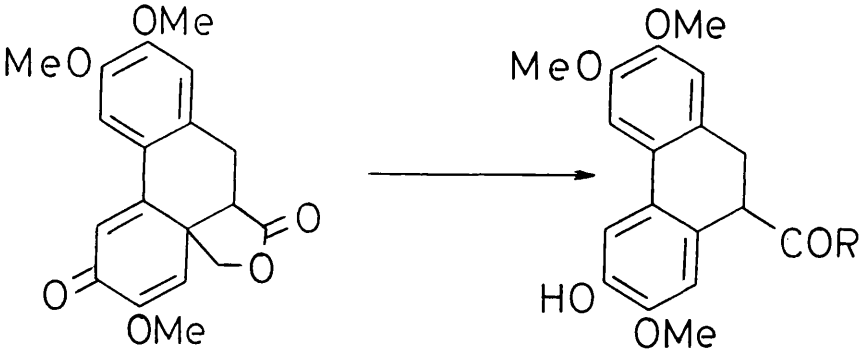
protons. The required "planar-W" coupling pathway is present in the alcohol (94) but not in alcohol (88). The constitution of this lactone with the coupling constants is shown below.



(94) (^{1}H n.m.r. data in δ , (coupling constants)).

A further consequence of the above reassignments is that the initial chemistry carried out upon the spirodienone (90)[37] is also subject to a re-examination. Ring opening experiments[37] with methanol/hydrochloric acid, ethanol/hydrochloric acid and

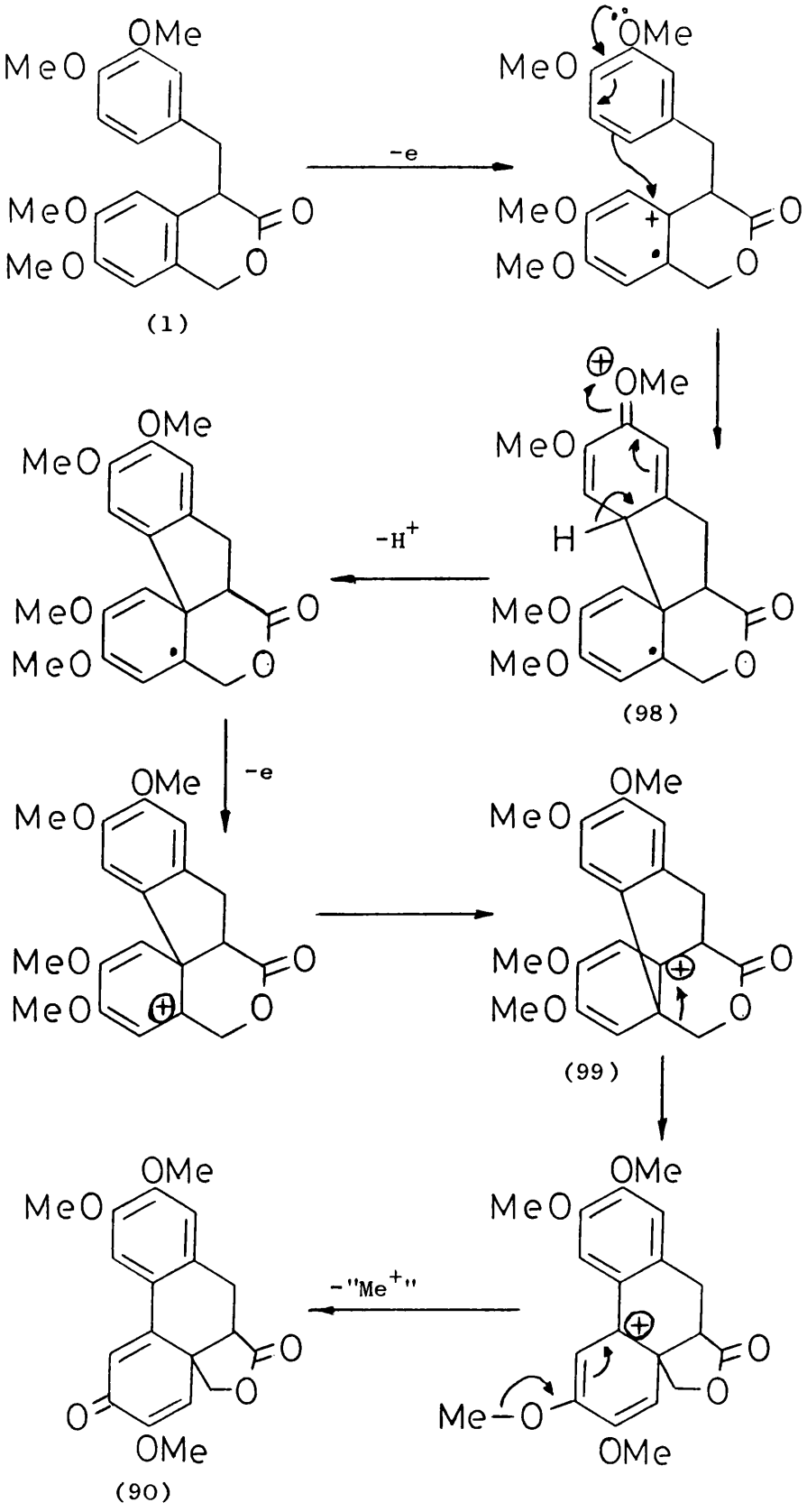
methylamine now give the following products, the methyl ester (95), the ethyl ester (96) and the amide (97) respectively.



(90)

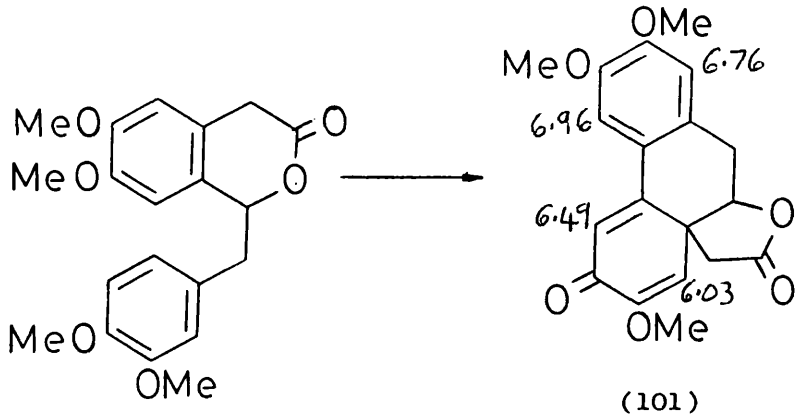
(95, R = OMe)
(96, R = OEt)
(97, R = NHMe)

The mechanism[21,42,53,54] of the formation of the spirodienone (90) may be described as an initial oxidation of the aryl ring of the isochromanone, followed by nucleophilic attack by the benzyl substituent (or vice versa), this gives an intermediate 5-membered radical cation species (98). The radical cation (98) undergoes firstly a deprotonation and secondly an oxidation followed by rearrangement to form the carbocation (99), the final s tep being demethylation to form the spirodienone (90).


OMe
MeO
MeO
MeO
O
O
(1)
-e
+
H
-H+
(98)
-e
(99)
-"Me+"
Me
OMe
(90)

Alternatively ring closure on to position 8a of the isochromanone ring is possible, followed by a ring contraction with concommitant de-O-methylation, which process is responsible will be investigated by subsequent workers. In either event the rearranged product (90) is formed - rather a surprising result when such a product is more strained than the spirodienone (2) which was for so long assumed to be the correct formulation.

However, this conversion of the lactone (1) to the spirodienone (90) parallels work by Elliot[55], who synthesised the corresponding 1-benzylisochroman-3-one (100) and oxidised it using vanadium trifluoride oxide, in both instances the product was the dienone (101). In his experimental Elliot incorrectly assigned the proton signals on the dienone ring of his product and set against our own experience my supervisor had previously viewed Elliots work with some suspicion. Now Elliots work is obviously correct and if the chemical shift data he presented is reassigned as shown in formula (101), a close correlation between the two products is revealed.

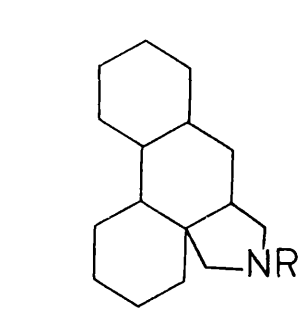


(100) (101)

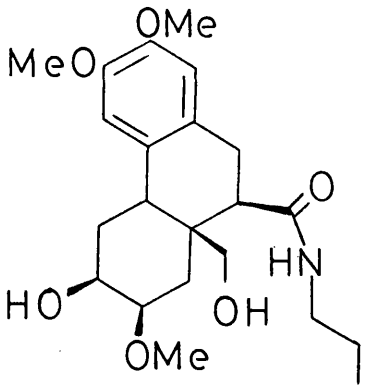
(^{1}H n.m.r. data in δ)

Following the hydrogenation experiments on the spirodienone (90) we carried out several attempted reductions using sodium cyanoborohydride in acidic media[20], noting that the lactone group is reported to be stable to these conditions[56]. In all cases the starting material was returned. The above series of compounds derived from the spirodienone (90) does not allow a direct conversion into the 4a,10-(methaniminomethano)-9,10-dihydrophenanthrene ring system, but still lead to useful precursors of a new ring system namely the 9,9a-(methaniminomethano)-9,10-dihydrophenanthrene system (102). This assembly

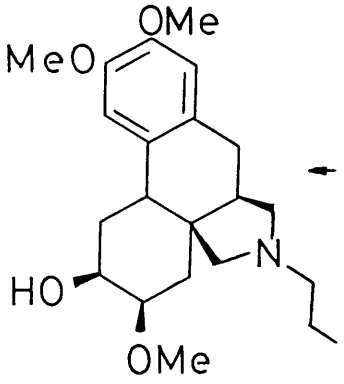
should be available by direct reduction of the amide (91) forming the amine (103), which then should ringclose to the tetracycle (104).



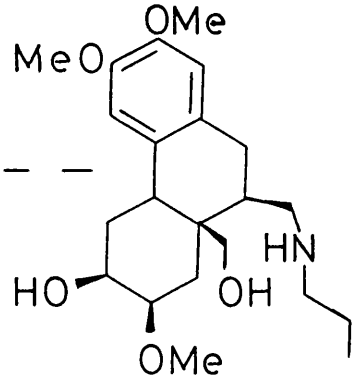
(102)



(91)



(104)

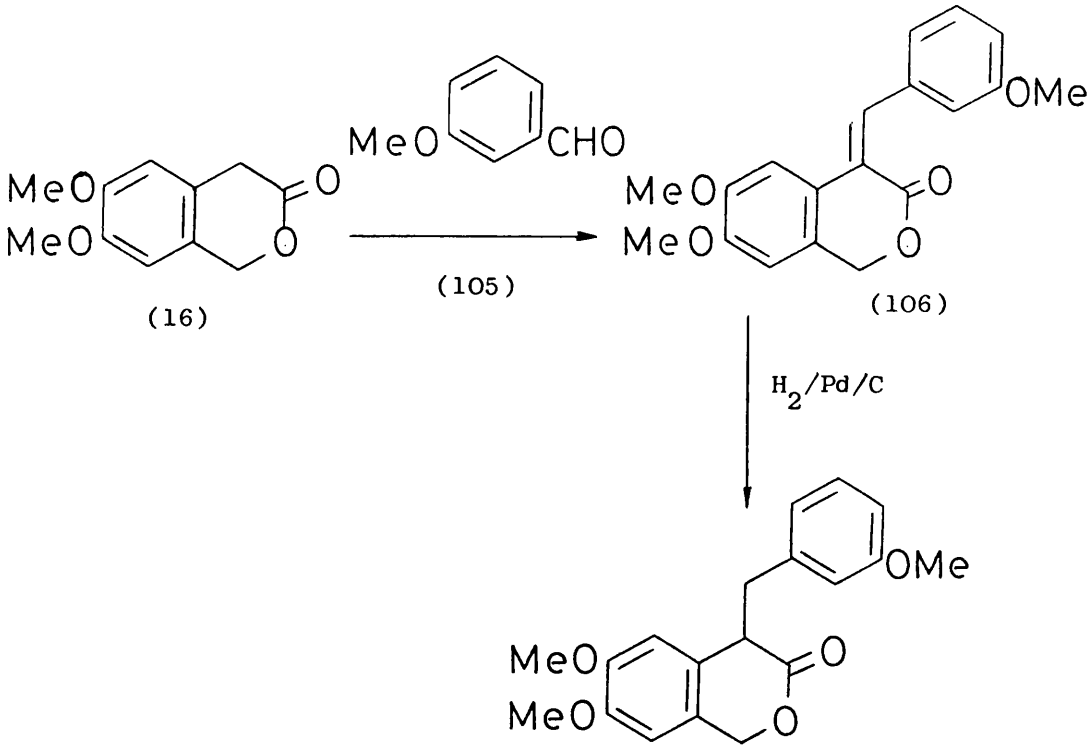


(103)

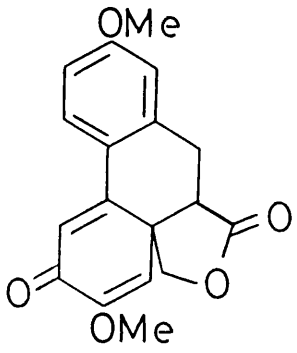
The first step in this sequence, i.e the amide to amine reduction was first attempted by the use of lithium aluminium hydride in boiling tetrahydrofuran, but the amide (91) proved more or less inert to these conditions. However, the amine (103) was eventually produced by using borane in boiling tetrahydrofuran[57]. We had expected the amine (103) to dehydrate spontaneously and ring close but in practice this did not occur. Clearly this should not prove a difficult step to achieve and there are several precedents already in the literature[58,59] but we had no further time left to investigate this problem.

In a parallel series of reactions the lactone (16) was condensed with 3-methoxybenzaldehyde (105) in the presence of piperidine, to furnish the benzylidene derivative (106) in low yield ($\sim$ 40%). The conditions for this reaction were the same as those used in the formation of the dimethoxylated analogue (26) but this last compound was formed in a much higher yield ($\sim$ 70%) we have no firm conclusions why this is so. Hydrogenation of the benzylidene derivative (106) in ethyl acetate and 10% palladium on charcoal yielded the lactone (107) in almost quantitative yield.

The electrochemical oxidation of the lactone (107) should prove interesting in view of the results based upon the oxidation of the lactone (1). If the same mechanism is



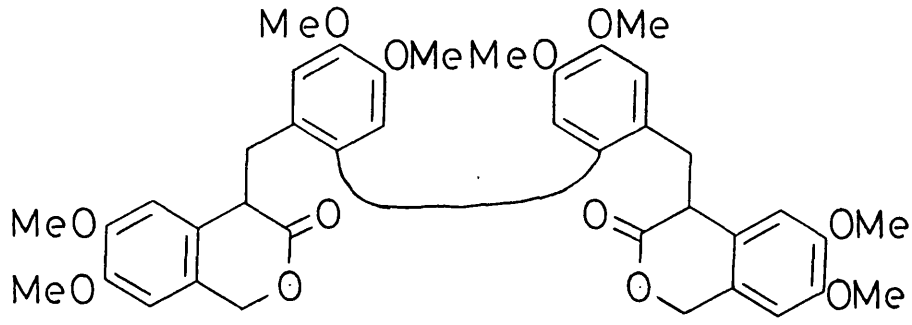
involved (see p. 82) as in the lactone (1) case then oxidation of the lactone (107) should produce the spirodienone (108).



(108)

Again due to lack of time this oxidation was not undertaken, but will be continued by other workers in this laboratory along with the oxidation of related structures in which the isochromanone ring is monomethoxylated. The results from these experiments may throw light upon the regioselectivity of the aryl-aryl process.

During the work on the electrochemical oxidation of the lactone (1) an alternative chemical oxidation was attempted namely with vanadium trifluoride oxide (VOF_3) in acetonitrile/dichloromethane. Small scale reactions employing up to one gram of substrate yielded dimeric products which were shown to be linked via the 6' position of the benzyl substituent (from n.m.r., mass spectral data, see expl. p. 126). These dimeric products (86) were also produced when the lactone (1) was electrolysed at high substrate concentration (see p. 74). Large scale chemical oxidations on the lactone (1) again yielded the dimeric products (86) as the major products but some spirodienone (90) was also produced in low yield. This mirrors the results of Elliot[55] who was able to produce the spirodienone (101) by both electrochemical and vanadium trifluoride oxide oxidations (see p. 83).



(86)

The dimeric products (86) could be partially separated by fractional crystallisation to give two diastereomers.

EXPERIMENTAL

Melting points are uncorrected. ^{1}H n.m.r. spectra were recorded at 100 MHz, unless otherwise stated, using a Jeol JNM-PS-100 spectrometer. 90 MHz and 250 MHz were obtained from the analytical services department of Glaxo Group Research (Ware). ^{13}C n.m.r. spectra were obtained using a Jeol FX90Q spectrometer at 25.2 MHz. I.R. spectra were taken as nujol mulls, unless otherwise stated, using a Perkin-Elmer 257 or 197 spectrometer. Ultra-violet spectra were obtained using a Perkin-Elmer 402 U.V.-Vis. spectrophotometer, in 95% ethanol solution. Mass spectra were obtained using a A.E.I. M.S. 12 instrument. Accurate mass measurements were obtained from P.C.M.U. Harwell (Didcot) and Glaxo Group Research (Ware). Analytical data were obtained from either Glaxo Group Research (Ware) or Butterworth Laboratories, Teddington. Dry solvents were obtained using standard literature methods[60-64].

4-(3,4-Dimethoxybenzyl)-6,7-dimethoxyisochroman-3-one (1)

4-(3,4-Dimethoxybenzylidene)-6,7-dimethoxyisochroman-3-one (26) (2.0 g, 0.005 mol) in glacial acetic acid (100 cm^3) was hydrogenated at atmospheric pressure in the presence of 10% palladium on charcoal (0.1 g). The solution was filtered through kieselguhr followed by evaporation of the solvent left a light brown oil which crystallized on standing to a white solid. Recrystallisation from ethanol yielded a white solid (1.8 g, 90%).

m.p. 106°C, (lit[2]., 104-105°C).

^{1}H n.m.r. (90 MHz, $CDCl_3$). δ 6.7 (d, 1H, 6'-H, J=8Hz), 6.56, 6.3 (2m, 4H, 4 x ArH), 4.95, 4.55 (AB, 2H, $ArCH_2O$, J=15Hz), 3.9 - 3.6 (m + 4s, 13H, 4 x OMe, ArCH), 3.14 (d, 2H, $ArCH_2$, J=6Hz).

^{13}C n.m.r. (DMSO). 172.0 (s, C=O), 148.6, 148.4, 147.8, 147.6 (s, 6-C, 7-C, 3'-C, 4'-C), 130.2 (s, 1'-C), 125.9 (s, 8a-C), 123.8 (s, 4a-C), 121.1 (d, 6'-C), 113.2 (d, 8-C), 111.7, 110.8, 108.4 (d, 5-C, 2'-C, 5'-C), 68.7 (t, $ArCH_2O$), 55.6, 55.5, 55.3 (q, 4 x MeO), 46.1 (d, $CH-CH_2$), 39.6 (t, CH_2-CH).

I.R. ν_{max}, 1730 (lactone)cm^{-1}.

U.V. λ_{max} (ε) nm., 213 (19550), 285 (6340).

Mass, m/e, 358 (M^+, 8%), 151 (100).

Found: C, 66.86; H, 6.21. Calc. for $C_{20}H_{22}O_6$: C, 67.03; H, 6.19%.

1,4-Dihydro-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)-2-methyl-3(2H)-isoquinolone (3).

6,7-Dimethoxy-4-(3,4-dimethoxybenzyl)-2-methyl-3-oxo-2H-isoquinolinium chloride (34) (0.8 g, 0.002 mol) was suspended in A.R. acetone (200 cm^3) and hydrogenated at 100 p.s.i. in the presence of Adams' catalyst (0.1 g) for 3 days. The mixture was filtered through kieselguhr and the solvent removed by evaporation to yield a green gum, which was chromatographed over silica using ethylacetate as the eluant, to afford the title compound as a colourless gum (0.58 g, 80%).

^{1}H n.m.r. ($CDCl_3$). δ , 6.66 (d, 1H, 5'-H, J=8Hz), 6.45 (s, 2H, 5-H, 8-H), 6.33 (dd, 1H, 6'-H, J=8, 2Hz), 6.19 (d, 1H, 2'-H, J=2Hz), 3.94-2.92 (ABX, 3H, CH_2-CH), 3.8 (s, 12H, 4 x MeO), 3.6 (s, 2H, $ArCH_2N$), 2.92 (s, 3H, N-Me).

I.R.(film). ν_{max}, 1640, 1600 cm^{-1}.

U.V. λ_{max} nm, 225, 280.

Mass, found: M^+, 371.1736. $C_{21}H_{25}NO_5$ requires: M^+, 371.1739.

m/e, 371 (M^+, 6%), 220 (42), 151 (100).

Electrochemical oxidation of 1,4-dihydro-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)-2-methyl-3(2H)-isoquinolone (3).

The lactam (3) (0.5 g, 0.0013 mol) in 0.0001 mol cm^{-3} anhydrous sodium perchlorate in dry acetonitrile (110 cm^3) was electrolysed at an anode potential of 1.2V (vs SCE.) at room temperature, using a platinum gauze anode and a mercury pool cathode. After all the starting material had been oxidised ($\sim$ 4h.), the anolyte was separated, water (10 cm^3) was added and the mixture evaporated to near dryness. The dark residue was dissolved in dichloromethane (80 cm^3), washed with brine (2 x 30 cm^3) and finally dried (Na_2SO_4). Removal of the solvent by evaporation left a brown gum which was shown to be a tarry residue (TLC., ^{1}H n.m.r., I.R.).

As a variant of this experiment, the above conditions were used again, but the electrochemical cell was kept at a temperature of 0-2^{o}C during the oxidation. The result was as above i.e. polymeric tarry residues.

Attempted condensation between 6,7-dimethoxy-2-methyl-1,4-dihydro-3(2H)-isoquinolone (5)[3] and veratraldehyde (9).

The following example is typical of the many attempts at this reaction in which nearly all the reaction parameters were varied. The two work-up procedures were the two types used throughout this series of experiments.

The whole of the following sequence was carried out under dry nitrogen. Potassium hydride (0.038 g, 0.0009 mol) was covered with dry tetrahydrofuran (THF) (3 cm^3) and cooled to -30°C, hexamethyldisilazane (0.15 g, 0.0009 mol) in THF (6 cm^3) was slowly added and the resultant mixture was stirred at -30°C for 0.5h. This solution was slowly added to a precooled solution (-78°C) of 6,7-dimethoxy-2-methyl-1,4-dihydro-3(2H)-isoquinolone (5)[3] (0.13 g, 0.0006 mol) in THF (10 cm^3) and dry N,N-dimethylformamide (DMF) (10 cm^3). After stirring at -78°C for 1h, 3,4-dimethoxybenzaldehyde (9) (0.16 g, 0.0009 mol) in THF (10 cm^3) was added dropwise over a period of 0.5h. The mixture was stirred for 2h. at -78°C and then warmed to 0°C.

Work-up A.

Saturated ammonium chloride solution (30 cm^3) was added to the solution, followed by extraction with dichloromethane (4 x 15 cm^3). The combined organic extracts were washed with brine (2 x 20 cm^3), dried (Na_2SO_4), and evaporated *in vacuo* to leave a yellow oil. Analysis of this oil showed the presence of the starting materials and some decomposed material (^1H n.m.r., I.R., Mass, T.L.C.).

Work-up B.

10% palladium on charcoal (0.15 g) was added to the solution and the mixture was hydrogenated at atmospheric pressure and room temperature for 24h. The mixture was filtered through celite, washed with brine (2 x 20 cm^3), dried (Na_2SO_4) and the solvent removed by evaporation to leave a yellow oil. Analysis of this oil showed the presence of the starting materials and some decomposed material (^1H n m.r., I.R., Mass, T.L.C.).

6,7-Dimethoxyisochroman-3-one (16)

3,4-Dimethoxyphenylacetic acid (68 g, 0.347 mol) in glacial acetic acid (140 cm^3) was heated to 60°C and conc. hydrochloric acid (50 cm^3) was added. This was followed by 37% formalin (50 cm^3) and the yellow solution was heated at 90°C for a further 1.25h. After cooling the dark solution was poured into cold water (1000 cm^3) and extracted with chloroform (4 x 200 cm^3). The combined organic extracts were washed with saturated sodium bicarbonate solution until neutral, then with water (2 x 400 cm^3) and finally dried ($MgSO_4$). Evaporation of the solvent afforded an off white solid which was recrystallised from ethanol to form white needles (48 g, 66%).

m.p. 104°C, (lit.[10], 106-108 °C).

^1H n.m.r. ($CDCl_3$). δ 6.75, 6.70 (2s, 2H, ArH), 5.25 (s, 2H, $ArCH_2O$), 3.90 (s, 6H, 2 x MeO), 3.65 (s, 2H, $ArCH_2CO$).

^{13}C n.m.r. (DMSO). δ 171.0 (s, C=O), 149.0, 147.8 (s, 6-C, 7-C), 124.1 (s, 8a-C), 123.6 (s, 4a-C), 110.8 (d, 8-C), 109.1 (d, 5-C), 69.3 (t, $\underline{C}H_2O$), 55.7 (q, 2 x MeO), 35.2 (t, $\underline{C}H_2CO$).

I.R. γ_{max}, 1730 (C=O), 1620 cm^{-1}.

Mass, m/e 208 (M^+ 100%), 164 (77), 151 (16), 149 (26), 121 (35).

2-(2-hydroxymethyl-4,5-dimethoxyphenyl)-N-methylethanamide (18).

6,7-Dimethoxyisochroman-3-one (16) (6.8 g, 0.032 mol) and 33% methylamine in ethanol (150 cm^3) were heated at reflux for 3h. Evaporation of the solvent left an off white solid which was recrystallised from ethanol to yield colourless prisms (6.5 g, 85%).

m.p. 120°C.

^{1}H n.m.r. ($CDCl_3$). δ 7.63 (nump, 1H, NH), 6.9, 6.82 (2s, 2H, 2 x ArH), 5.32 (t, 1H, OH, J=6Hz), 4.54 (d, 2H, $C\underline{H}_2OH$, J=6Hz), 3.83 (s, 6H, 2 x MeO), 3.5 (s, 2H, $ArC\underline{H}_2CO$), 2.68 (d, 3H, NMe, J=5Hz).

^{13}C n.m.r. (DMSO), δ 171.1 (s, C=O), 147.6, 147.4 (s, $\underline{C}$-OMe), 133.1 (s, $Ar\underline{C}$-CH_2OH), 126.2 (s, $Ar\underline{C}$-CH_2CO), 114.3 (d, 3-C), 112.5 (d, 6-C), 61.0 (t, CH_2OH), 55.5 (q, MeO), 38.8 (t, $\underline{C}H_2CO$), 25.6 (q, NMe).

I.R. γ_{max}, 3300 (OH), 3150 (NH), 1630, 1610 (amide) cm^{-1}.

Mass, m/e 239 (M^+, 16%), 167 (26), 73 (100).

Found: C, 60.25; H, 6.89; N, 5.63. $C_{12}H_{17}NO_4$ requires: C, 60.24; H, 7.16; N, 5.85%.

Reaction between 2-(2-hydroxymethyl-4,5-dimethoxyphenyl)-N-methylethanamide (18) and triphenylphosphine/diethylazodicarboxylate

The hydroxyamide (18) (0.81 g, 0.003 mol) and triphenylphosphine (0.88 g, 0.003 mol) in dry tetrahydrofuran (THF) (160 cm^3) were stirred under a dry nitrogen atmosphere. Diethylazodicarboxylate (0.6 g, 0.003 mol) in dry THF (3 cm^3) was added dropwise. The solution was stirred at room temperature for 24h. and the solvent removed by evaporation to leave a red-brown oil. Analysis of this oil showed it to be a multicomponent mixture (^1H n.m.r., I.R., T.L.C.).

Reaction between 2-(2-hydroxymethyl-4,5-dimethoxyphenyl)-N-methylethanamide (18) and methanesulphonyl chloride/triethylamine

The hydroxyamide (18) (0.5 g, 0.002 mol) in dry pyridine (30 cm^3) was cooled to 0^oC under a dry nitrogen atmosphere. Freshly distilled methanesulphonyl chloride (0.3 g, 0.0026 mol) was added dropwise with stirring over a period of 0.25h. Triethylamine (0.2 g, 0.002 mol) in dry pyridine (5 cm^3) was added dropwise over a period of 0.25 h. The mixture was stirred at 0^oC for 1h., then room temperature for 2h. The solvent was removed by evaporation and the residue dissolved in dichloromethane (10 cm^3), washed with dilute hydrochloric acid (2 x 8 cm^3), brine (2 x 8 cm^3) and finally dried ($MgSO_4$). Evaporation of the solvent left a yellow oil which was chromatographed over silica using dichloromethane/ethyl acetate to yield 6,7-dimethoxyisochroman-3-one (16) as a white solid (0.1 g, 24%), which was identical with a sample of (16) prepared by an alternative route (see p.94).

2-(2-Hydroxymethyl-4,5-dimethoxyphenyl)-ethanohydrazide (20).

6,7-Dimethoxyisochroman-3-one (16) (22.3 g, 0.1 mol) in absolute ethanol (500 cm^3) and freshly distilled hydrazine (4 g, 0.125 mol) were heated at reflux for 7h. Evaporation of the solvent and excess reagent left an off white solid which was recrystallised from methanol (15.5 g, 60%).

m.p. 163°C, (lit.[13], 163-165°C).

^{1}H n.m.r. ($CDCl_3$/DMSO, 20:1). δ 8.95 (br.s, 1H, NH*), 6.88, 6.84 (2s, 2H, 2 x ArH), 5.13 (br.s, 1H, OH*), 4.57 (br.s, 2H, $\underline{CH}_2$-OH), 3.86 (s, 6H, 2 x MeO), 3.53 (s, 2H, $\underline{CH}_2$-CO), 2.86 (br.s, 2H, NH_2*). (H* removed by D_2O).

^{13}C n.m.r. ($CDCl_3$ + DMSO). δ 170.4(s, C=O), 147.7, 147.5 (s, $\underline{C}$-OMe), 133.1 (s, $\underline{C}$-CH_2OH), 126.2 (s, $\underline{C}$-CH_2CO), 114.1 (d, 3-C), 112.8 (d, 6-C), 61.4 (t, $\underline{CH}_2OH$), 55.6 (q, 2 x MeO), 37.1 (t, $\underline{CH}_2$-CO).

I.R. ν_{max}, 3325 (NH), 3250 (OH), 1685, 1610 (amide)cm^{-1}.

Mass. m/e, 240 (M^+, 7%), 222 (100), 208 (39), 191 (73), 181 (42), 167 (31).

Found: C, 54.91; H, 6.77; N, 11.54. Calc for $C_{11}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.66%.

Bis-2,2-(6,7-dimethoxy-1,4-dihydro-3(2H)-isoquinolonyl) (22)

2-(2-Hydroxymethyl-4,5-dimethoxyphenyl)ethanohydrazide (20) (5 g, 0.02 mol) in 10% hydrochloric acid (200 cm^3) was heated at reflux for 2h. After cooling water (50 cm^3) was added and the white solid obtained by filtration, crystallisation from ethanol was followed by recrystallisation from toluene to give the product as colourless needles (3.1g, 75%).

m.p. 215°C, (lit.[13], 227-228°C).

^{1}H n.m.r. (DMSO). δ, 6.87, 6.84 (2s, 4H, 4 x ArH, 5-H, 8-H, 5'-H, 8'-H), 4.58 (s, 4H, 2 x ArCH_2N), 3.76 (s, 12H, 4 x MeO), 3.67 (s, 4H, 2 x ArCH_2CO).

^{13}C n.m.r. (TFA). δ 174.2 (s, C=O), 150.7, 150.0 (s, C-OMe), 123.7, 123.4 (s, 4a-C, 8a-C, 4a'-C, 8a'-C), 112.9 (d, 8-C, 8'-C), 111.1 (d, 5-C, 5'-C), 57.3, 57.2 (q, 4 x MeO), 53.2 (t, 1-C, 1'-C), 37.2 (t, 4-C, 4'-C).

I.R. ν_{max}, 1660, 1610 cm^{-1}.

Mass, m/e, 412 (M^+, 2%), 207 (22), 97 (21), 71 (100).

Found: C, 63.82; H, 5.91; N, 6.65. Calc. for $C_{22}H_{24}N_2O_6$: C, 64.07; H, 5.87; N, 6.79%.

4-(3,4-Dimethoxybenzylidene)-6,7-dimethoxyisochroman-3-one (26).

6,7-Dimethoxyisochroman-3-one (16) (16.7 g, 0.08 mol), 3,4-dimethoxybenzaldehyde (9) (13.4 g, 0.08 mol) and pyrrolidine (3.5 cm^3) were heated under a dry nitrogen atmosphere at 140°C for 2.5h. The cool gum had 10% acetic acid in ethanol (20 cm^3) added, the gum-solid was crushed and crystallised from absolute ethanol. Recrystallisation from absolute ethanol yielded fine yellow needles (17.2 g, 60%).

m.p. 175-176°C, (lit.[2], 176-177°C).

^{1}H n.m.r. ($CDCl_3$), δ 7.71 (s, 1H, vinyl H), 7.15 (dd, 1H, 6'-H, J=8, 2Hz), 7.11, 7.01 (2s, 2H, 8-H, 2'-H), 6.82 (d, 1H, 5'-H, J=8Hz), 6.74 (s, 1H, 5-H), 5.29 (s, 2H, ArCH_2), 3.91, 3.75, 3.58 (3s, 12H, 4 x OMe).

^{13}C n.m.r. (DMSO). δ 167.8 (s, C=O), 150.1, 149.1, 148.4, 147.8

(s, 6-C, 7-C, 3'-C, 4'-C), 135.4 (s, 4-C), 126.6, 126.1, 123.2 (s, 4a-C, 8a-C, 1'-C), 122.7, 122.1 (d, 6'-C, ArCH=C), 113.0 (d, 8-C), 111.6, 109.8, 108.9 (d, 4-C, 2'-C, 5'-C), 68.4 (t, $ArCH_2O$), 55.5, 55.4, 55.2 (q, 4 x MeO).

I.R. ν_{max}, 1720 (C=O) cm^{-1}

Mass, m/e 356 (M^+, 22%), 279 (18), 261 (41), 113 (100).

Found: C, 67.49; H, 5.76. Calc. for $C_{20}H_{20}O_6$: C, 67.41; H, 5.66%.

Ethyl-2-(2-ethoxymethyl-4,5-dimethoxyphenyl)-3-(3,4-dimethoxyphenyl)propanoate (31).

A solution of 4-(3,4-dimethoxybenzyl)-6,7-dimethoxyisochroman-3-one (1) (7 g, 0.019 mol) in absolute ethanol (160 cm^3) containing concentrated hydrochloric acid (2 cm^3) was heated at reflux for 8h. The cool solution was evaporated to near dryness, then taken up in dichloromethane (60 cm^3), which was washed with saturated sodium bicarbonate solution (60 cm^3), water (2 x 50 cm^3) and finally dried ($MgSO_4$). Removal of the solvent left a yellow oil which was chromatographed over silica using ethyl acetate as the eluant, to give the title compound as a colourless gum (5.2 g, 63%).

^1H n.m.r. (250 MHz, $CDCl_3$). δ, 7.08, 6.82 (2s, 2H, 3-H, 6-H), 6.8-6.6 (m, 3H, 2'-H, 5'-H, 6'-H), 4.48, 4.26 (AB, 2H, CH_2OEt), 4.18 (ABX, 1H, $CH-CH_2$), 4.2-4.0 (m, 2H, $COOCH_2Me$), 3.94-3.8 (4s, 12H, 4 x MeO), 3.5 (2q, 2H, CH_2OCH_2Me), 3.34, 2.95 (ABX, 2H, CH_2-CH), 1.25 (t, 3H, $COOCH_2CH_3$), 1.16 (t, 3H, $CH_2OCH_2CH_3$).

I.R. (film). ν_{max}, 2940, 2840, 1730 (ester), 1605, 1595, cm^{-1}.

U.V. λ_{max} nm, 230, 280.

Mass, m/e, 432 (M^+, 16%), 386 (24), 313 (28), 195 (24), 151 (100).

Attempted lactone ring opening experiments between 4-(3,4-dimethoxybenzyl)-6,7-dimethoxyisochroman-3-one (1) and (a) methanol/potassium carbonate, and (b) isobutene/concentrated sulphuric acid.

(a) A solution of the lactone (1) (0.1 g, 0.0003 mol) and anhydrous potassium carbonate in A.R. methanol (20 cm^3) were heated at reflux under a dry nitrogen atmosphere for 24h. The cool solution was poured into water (50 cm^3) and extracted with dichloromethane (4 x 10 cm^3), the combined organic extracts were washed with water (20 cm^3), dilute hydrochloric acid (2 x 20 cm^3), brine (20 cm^3) and finally dried ($MgSO_4$). Removal of the solvent by evaporation left an off white solid, which was shown to be starting material (^1H n.m.r., T.L.C., I.R., Mass).

(b) The lactone (1) (0.1 g, 0.0003 mol) in dichloromethane (10 cm^3) was added to a Schlenck tube, after cooling to 0^oC liquid isobutene (20 cm^3) was added, followed by concentrated sulphuric acid (1 cm^3). The mixture was mechanically shaken (behind a blast screen) for 24h. The tube was carefully opened and the contents poured out, dichloromethane (10 cm^3) was added to the tube and this was mixed with the initial contents. The mixture was washed with saturated sodium bicarbonate solution (2 x 20 cm^3), water (2 x 20 cm^3) and finally dried ($MgSO_4$). Removal of the solvent by evaporation left an off white solid, which was shown to be starting material (^1H n.m.r., T.L.C., I.R., Mass).

Various other attempts at this experiment were conducted using no solvent, and other solvents e.g. ethylene glycol, in each case only starting material was recovered.

4-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-2-methyl-3-oxo-2H-isoquinolinium chloride (34).

N,N-Dimethyl-2-(2-formyl-4,5-dimethoxyphenyl)-3-(3,4-dimethoxyphenyl)propionamide (36) (2.6 g, 0.006 mol) in 33% methylamine in ethanol (100 cm^3) was heated at reflux for 6h. Evaporation of the solvent and excess reagent left a green gum which was dissolved in hot 6M-hydrochloric acid (50 cm^3). On cooling the salt separated as white needles (1.97 g, 75%).

m.p. 180°C (dec.) (lit.[3], 140 - 150°C).

^{1}H n.m.r. (CF_3COOH). δ 7.46, 7.32 (2s, 2H, 5-H, 8-H), 7.0, 6.9 (m, 2H, 2 x ArH), 6.9 (s, 1H, 1-H), 6.71 (d, 1H, ArH, J=9Hz), 4.66 (s, 2H, $ArCH_2$), 4.4 (s, 3H, N^+Me), 4.20, 4.12, 4.00, 3.94 (4s, 12H, 4 x MeO).

I.R. ν_{max} 1640, 1600 cm^{-1}

U.V. λ_{max} (ε) nm, 256 (53600).

Found: C, 62.0; H, 5.8; N, 3.2. Calc. for $C_{21}H_{24}NO_5Cl$: C, 62.1; H, 6.0; N, 3.4%.

Reduction of 4-(3,4-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-3-oxo-2H-isoquinolinium chloride (34) by sodium cyanoborohydride

The salt (34) (0.079 g, 0.0002 mol) was dissolved in A.R. methanol (12 cm^3) and sodium cyanoborohydride (0.029 g, 0.0004 mol) in methanol (4 cm^3) was added. The solution was made acid by the

addition of dilute hydrochloric acid until the mixture was pH ~ 4. After stirring at room temperature for 24h. the solution was poured into water (50 cm^3) and extracted with dichloromethane (4 x 10 cm^3). The combined organic extracts were washed with water (2 x 20 cm^3) and dried (Na_2SO_4). Removal of the solvent by evaporation left a yellow gum which was a complex mixture as shown by (T.L.C., I.R., ^1H n.m.r.).

3-(3,4-Dimethoxyphenyl)-2-(2-hydroxymethyl-4,5-dimethoxyphenyl)-N,N-dimethylpropionamide (35).

4-(3,4-Dimethoxybenzyl)-6,7-dimethoxyisochroman-3-one (1) (11.74 g, 0.032 mol) and 33% dimethylamine in ethanol (200 cm^3) were heated at reflux for 30h. Evaporation of the solvent and excess reagent left a yellow oil which crystallised on cooling. Recrystallisation from ethanol afforded colourless prisms (8.7 g, 66%).

m.p. 135°C, (lit.[3], 134 - 135°C).

^1H n.m.r. ($CDCl_3$). δ 7.08, 6.79 (2s, 2H, 3-H, 6-H), 6.70, 6.51 (2m, 3H, 2'-H, 5'-H, 6'-H), 4.37 (br.s, 2H, CH_2OH), 4.23 (t, 1H, $CH-CH_2$, J=7Hz), 3.87, 3.84, 3.82, 3.68 (4s, 12H, 4 x MeO), 3.35 (dd, 2H, CH_2-CH, J=15, 7Hz) 2.90 (br.s, 6H, NMe_2), 1.80 (hump, 1H, OH removed by D_2O).

^{13}C n.m.r. (DMSO). δ 172.3 (s, C=O), 148.3, 148.0, 147.2 (s, 4 x C-OMe), 132.8 (s, 2-C), 131.8, 130.1 (s, 1-C, 1'-C), 120.9 (d, 6'-C), 113.2 (d, 3-C), 112.6, 111.7, 111.0 (d, 6-C, 2'-C, 5'-C), 60.8 (t, $ArCH_2OH$), 55.5, 55.3 (q, 4 x MeO), 44.9 (d, CH-CO), 39.5 (t, CH_2-CH), 36.3, 35.3 (q, NMe_2).

I.R. $\hat{\nu}_{max}$, 3380, 1620 cm^{-1}.

U.V. λ_{max} (ε) nm, 242 (8460), 281 (5860).

Mass, m/e, 403 (M^+ 37%), 385 (16), 313 (99), 179 (98), 151 (100).

Found: C, 65.30; H, 7.19; N, 3.38. Calc. for $C_{22}H_{29}NO_6$: C, 65.5; H, 7.2; N, 3.5%.

N,N-Dimethyl-2-(2-formyl-4,5-dimethoxyphenyl)-3-(3,4-dimethoxyphenyl)propionamide (36).

N,N-Dimethyl-2-(2-hydroxymethyl-4,5-dimethoxyphenyl)-3-(3,4-dimethoxyphenyl)propionamide (35) (9.8 g, 0.024 mol) was added to a stirred suspension of pyridinium chlorochromate (9.0 g, 0.041 mol) in dry dichloromethane (200 cm^3). After stirring at room temperature for 1h. the mixture was filtered through celite and evaporated to an off white solid. This solid was chromatographed over silica using dichloromethane as the eluant to yield a white solid (8.6 g, 90%).

m.p. 102°C, (lit.[3], 104 - 105°C).

^{1}H n.m.r. ($CDCl_3$). δ 9.85 (s, 1H, CHO), 7.24, 7.19 (2s, 2H, 2 x ArH, 2-H, 6-H), 6.71 (br.s, 3H, 3 x ArH, 2'-H, 5'-H, 6'-H), 5.38 (t, 1H, C<u>H</u>-CH_2, <u>J</u>=7Hz), 3.98, 3.93, 3.82, 3.80 (4s, 12H, 4 x MeO), 3.38 (dd, 2H, $C\underline{H}_2$-CH, <u>J</u>=14, 7Hz), 2.90, 2.76 (2s, 6H, NMe_2).

^{13}C n.m.r. (DMSO). δ 191.2 (d, CHO), 171.9 (s, C=O), 153.6, 148.4, 147.7, 147.4 (s, <u>C</u>-OMe), 136.3 (s, <u>C</u>-CHO), 131.9, 126.3 (s, 1-C, 1'-C), 121.2 (d, 6'-C), 114.0 (d, 3-C), 113.4, 111.7, 110.8 (d, 6-C, 2'-C, 5'-C), 55.7, 55.6, 55.5, 55.4 (q, 4 x MeO), 42.9 (d, <u>C</u>H-CH_2), 39.7 (t, $\underline{C}H_2$-CH), 36.4, 35.5 (q, NMe_2).

I.R. ν_{max}, 1680 (CHO), 1625 (amide) cm^{-1}.

U.V. λ_{max} (ε) nm, 243 (11,600), 283 (9960), 310 (5780).

Mass, m/e 401 (M^+, 1%), 383 (41), 311 (6), 151 (100).

Found: C, 65.4; H, 6.9; N, 3.5. Calc for $C_{22}H_{27}NO_6$: C, 65.8; H, 6.8; N, 3.5%.

2-Formyl-1,2,3,4-tetrahydro-6,7-dimethoxy-4-(3,4-dimethoxybenzyl) isoquinoline (38).

A solution of 1,2,3,4-tetrahydro-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)isoquinolinium hydrochloride (46) (0.7 g, 0.0018 mol) in formamide (30 cm^3) and formic acid (6 cm^3) were heated under reflux for 7h. The cooled solution was poured into water (100 cm^3) and extracted with dichloromethane (4 x 30 cm^3), the combined extracts were washed with water (2 x 50 cm^3), dried (Na_2SO_4) and evaporated to a yellow oil. The oil was chromatographed over silica using dichloromethane/ethylacetate as eluant to afford a white solid (0.5 g, 75%).

m.p. 115 - 117°C.

^{1}H n.m.r. ($CDCl_3$), δ 8.36, 8.07 (2s, 1H, CHO), 6.9 - 6.5 (m, 4H, 5-H, 2'-H, 5'-H, 6'-H), 6.44 (s, 1H, 8-H), 5.1, 4.21 (AB, 2H, $ArCH_2N$, J=12Hz), 4.0 - 3.54 (m, 1H, CH_2CHCH_2), 3.86, 3.78 (2s, 12H, 4 x MeO), 3.78 (m, 2H, NCH_2CH), 3.2 - 2.46 (m, 2H, $ArCH_2CH$).

I.R. ν_{max} 1660, 1610 (amide), 1585 cm^{-1}.

Mass, found: M^+, 371.1736. $C_{21}H_{25}NO_5$ requires: M^+, 371.1739.

m/e, 371 (M^+, 21%), 220 (74), 151 (100).

Found: C, 75.40; H, 5.21; N, 3.62. $C_{21}H_{25}NO_5$ requires: C, 75.17; H, 5.30; N, 3.51%.

Electrochemical oxidation of 2-formyl-1,2,3,4-tetrahydro-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)isoquinoline (38).

The amide (38), (0.497 g, 0.0013 mol) in 0.0001 mol cm^{-3} anhydrous sodium perchlorate in dry acetonitrile (110 cm^3), was electrolysed at an anode potential of 1.2V. (vs SCE.) at room temperature, using a carbon felt anode and a mercury pool cathode. After all the starting material had been oxidised ($\sim$ 2h.), the anolyte was separated, water (10 cm^3) was added and the mixture evaporated to near dryness. The dark residue was dissolved in chloroform (55 cm^3), washed with brine (2 x 20 cm^3) and finally dried (Na_2SO_4). Removal of the solvent by evaporation left a brown gum, which was chromatographed over silica using dichloromethane/ethyl acetate as the eluant. This process produced only tarry residues as shown by ^1H n.m.r., T.L.C., I.R.

2,2-Dimethoxy-N-(3,4-dimethoxybenzylidene)ethylamine (41).

Aminoacetaldehydedimethylacetal (40) (111.1 g, 0.66 mol) and 3,4-dimethoxybenzaldehyde (9) (70.4 g, 0.66 mol) in dry benzene (400 cm^3) were heated under reflux for 7h. with constant removal of water using a Dean and Stark trap. Evaporation of the solvent yielded a colourless oil which was triturated with cold absolute ethanol (10 cm^3). The crystalline product was recrystallised from absolute ethanol furnishing colourless needles (118.4 g, 70%).

m.p. 55 - 56°C, (lit.[5], 57 - 58°C).

^{1}H n.m.r. ($CDCl_3$). δ, 8.21 (br.s, 1H, ArCH-N), 7.46 (d, 1H, 2-H, J=2Hz), 7.19 (dd, 1H, 6-H, J=16, 2Hz), 6.88 (d, 1H, 5-H, J=16Hz), 4.69 (t, 1H, $(MeO)_2CH$, J=6Hz), 3.92 (2s, 6H, 2 x MeOAr), 3.78 (d, 2H, N-CH_2-CH, J=6Hz), 3.44 (s, 6H, $(MeO)_2CH$).

I.R. ν_{max}, 1640 (C=N) cm^{-1}.

Mass, m/e, 253 (M^+, 50%), 222(50), 190(36), 151 (100).

2,2-Dimethoxy-N-(3,4-dimethoxybenzyl)ethylamine (42).

2,2-Dimethoxy-N-(3,4-dimethoxybenzylidene)ethylamine (41) (96.6 g, 0.37 mol) in ethanol (600 cm^3) was treated with sodium borohydride (21.8 g, 0.57 mol) in portions over a period of 1h. After stirring at room temperature overnight, water (1200 mL) was added and the mixture extracted with dichloromethane (4 x 250 cm^3). The combined organic extracts were washed with water (2 x 300 cm^3) and dried (Na_2SO_4). Evaporation of the organic solvent left a yellow oil which was distilled (205°C at 0.6 mmHg) as a colourless oil (76.0 g, 80%). Lit.[5], b.p. 150 - 160°C at 0.6 mmHg.

^{1}H n.m.r. ($CDCl_3$). δ, 7.30 (s, 1H, 2-H), 7.0 - 6.7 (m, 3H, 2 x ArH + NH (removed by D_2O)), 4.70 (t, 1H, $(MeO)_2CH$, J=7Hz), 4.0 - 3.8 (3s, 8H, $ArCH_2$ + 2 x MeOAr), 3.40 (s, 6H, 2 x OMe), 2.80 (d, 2H, CH_2CH, J=7Hz).

I.R. (film). ν_{max}, 3530 - 3320 (NH), 2940, 2840, 1610 cm^{-1}.

Mass, m/e, 255 (M^+, 30%), 223 (35), 180(20), 151 (100).

6,7-Dimethoxy-4-(3,4-dimethoxybenzyl)isoquinoline (43).

Freshly distilled 2,2-dimethoxy-N-(3,4-dimethoxybenzyl)-ethylamine (42) (25.9 g, 0.1 mol) and 3,4-dimethoxybenzaldehyde (9) (17.3 g, 0.1 mol) were dissolved in 6N hydrochloric acid (40 cm^3) and absolute ethanol (40 cm^3). This mixture was heated on a steam bath for 2h., and when cool poured into cold water (100 cm^3), which was extracted with ether (2 x 100 mL). The aqueous phase was basified with 30% sodium hydroxide to pH 9, the resultant oily precipitate was separated by decantation and dissolved in dichloromethane (300 cm^3). The organic phase was washed with brine (2 x 150 cm^3), dried (Na_2SO_4) and finally evaporated to a dark brown oil. This oil was chromatographed over basic alumina using dichloromethane as the eluant to yield the product as an off white solid, which was crystallised from ethanol to afford fine white needles (10.1 g, 30%).

m.p. 126 - 127°C, (lit.[5], 126 - 128°C).

^{1}H n.m.r. ($CDCl_3$). δ, 9.03 (br.s, 1H, 1-H), 8.33 (s, 1H, 3-H), 7.20, 7.10 (2s, 2H, 5-H, 8-H), 6.8 - 6.6 (m, 3H, 2'-H, 5'-H, 6'-H), 4.20 (s, 2H, $ArCH_2$), 3.95, 3.84, 3.79, 3.72 (4s, 12H, 4 x MeO).

I.R. ($CHCl_3$). ν_{max}, 2830, 1595 cm^{-1}.

U.V. λ_{max} (ε) nm, 238 (57600), 282 (7900), 288 (sh. 7650), 313 (3400), 326 (3150).

Mass, m/e, 339 (M^+, 100%), 324 (19), 308 (11).

2-Benzyl-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)isoquinolinium bromide (44).

6,7-Dimethoxy-4-(3,4-dimethoxybenzyl)isoquinoline (43) (1g, 0.003 mol) and benzyl bromide (0.5 g, 0.003 mol) in acetone (100 cm^3) were stirred at room temperature for 24h. The salt was removed by filtration and recrystallised from ethanol to yield colourless prisms (0.9 g, 60%).

m.p. 126 - 128°C, (lit.[5], 127 - 130°C).

^{1}H n.m.r. (DMSO), δ, 9.97 (s, 1H, 1-H), 8.90 (s, 1H, 3-H), 7.97 (s, 1H, 8-H), 7.77 (s, 1H, 5-H), 7.8 - 7.5 (m, 5H, N-CH_2Ph), 7.1 (br.s, 1H, 2'-H), 6.98 (s, 2H, 5'-H, 6'-H), 6.02 (s, 2H, NCH_2Ph), 4.55 (br.s, 2H, ArCH_2), 4.13, 4.04, 3.77, 3.73 (4s, 12H, 4 x MeO).

I.R. ($CHCl_3$). ν_{max}, 2840, 1260, 1025 cm^{-1}.

U.V. λ_{max} (ε) nm, 258 (58300), 285 (sh), 319 (12400).

Mass, m/e, 339 (M^+-91, 29%), 91(100).

2-Benzyl-1,2,3,4-tetrahydro-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)-isoquinoline (45).

2-Benzyl-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)isoquinolinium bromide (44) (2 g, 0.004 mol) in ethanol (100 cm^3) was treated with sodium borohydride (0.5 g, 0.013 mol) in portions over 0.5 h. After stirring at room temperature overnight 2N hydrochloric acid (50 cm^3) was added, when the solution had become homogenous, 2N sodium hydroxide solution was added until the solution was alkaline to litmus. The cooled solution was

then extracted with dichloromethane (4 x 50 cm^3), the combined organic extracts were washed with water (2 x 100 cm^3) and finally dried (Na_2SO_4). Evaporation of the solvent left an oil which was crystallised from hot ethanol as colourless prisms (1.4 g, 80%).

m.p. 105 - 106° (lit.[5], 106 - 107°C.).

^{1}H n.m.r. ($CDCl_3$). δ, 7.5 - 7.2 (m, 5H, $NCH_2\underline{Ph}$), 6.8 - 6.5 (m, 5H, 5-H, 8-H, 2'-H, 5'-H, 6'-H), 3.9 - 3.5 (3s, 12H, 4 x MeO), 3.6 (br.s, 2H, $ArCH_2N$), 3.7 - 3.3 (AB, 2H, $PhCH_2N$, J=18Hz), 3.0 - 2.3 (m, 5H, $ArCH_2CHCH_2N$).

I.R. ν_{max}, 1605, 1590, 1510 cm^{-1}.

U.V. λ_{max} (ε) nm, 239 (8330), 283 (6710).

Mass, m/e 433 (M^+, 12%), 432 (21), 342 (100), 314 (10), 299 (16), 281 (62), 151 (21).

1,2,3,4-Tetrahydro-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)-isoquinolinium hydrochloride (46).

2-Benzyl-1,2,3,4-tetrahydro-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)isoquinoline hydrochloride (45) (1.4 g, 0.003 mol) was dissolved in absolute ethanol (400 cm^3) and hydrogenated at atmospheric pressure over 10% palladium on charcoal (0.1 g) for 24h. The mixture was filtered through kieselguhr and the solvent removed by evaporation to leave a white solid which was crystallised from ethanol as white needles (0.9 g, 88%).

m.p. 137°C, (lit.[5], 136 - 140°C).

^{1}H n.m.r. ($CDCl_3$). δ, 6.9 - 6.6 (m, 3H, 2'-H, 5'-H, 6'-H), 6.50 (s, 2H, 5-H, 8-H), 3.9 - 3 7 (m, 14H, 4 x OMe, and $ArCH_2N$), 3.0 - 2.8 (m, 5H, aliphatics).

I.R. ν_{max}, 2800 - 2300 (NH_2^+), 1590 cm^{-1}.

U.V. λ_{max} (ε) nm, 234 (15350), 282 (6300).

Mass, m/e, 343 (M^+, 32%), 192 (100), 161 (16), 151 (16).

3-(3,4-Dimethoxyphenyl)-2-(2-hydroxymethyl-4,5-dimethoxyphenyl) propionamide (53).

An ice cold solution of 4-(3,4-dimethoxybenzyl)-6,7-dimethoxyisochroman-3-one (1) (3 g, 0.008 mol) in absolute methanol (400 cm^3) was saturated with ammonia gas and left to stand at room temperature for 24h. Evaporation of the solvent left a yellow oil which was triturated with petroleum ether to give a white solid. Recrystallisation from ethyl acetate/ petroleum ether produced a white solid (3.1 g, 95%).

m.p. 108°C.

^1H n.m.r. (250 MHz, $CDCl_3$). δ 7.06 (s, 1H, ArH, 6-H), 6.7 - 6.55 (m, 4H, 3 x ArH, 2'-H, 5'-H, 6'-H, and 1 x NH), 6.51 (s, 1H, ArH, 3-H), 5.3 (br.s, 1H, NH), 4.5 (dd, 1H, CH-OH J=11, 6Hz), 4.3 (dd, 1H, CH-OH, J=11, 3Hz), 4.04 (t, 1H, CH-CO, J=7Hz), 3.88, 3.80, 3.79, 3.68 (4s, 12H, 4 x MeO), 3.38 (dd, 1H, ArCH-CH, J=13, 6Hz), 3.14 (br.s, 1H, OH), 2.94 (dd, 1H, ArCH-CH, J=13, 8.5Hz).

^{13}C n.m.r. (DMSO). δ 174.7 (s, C=O), 148.3, 147.8, 147.1 (s, 4 x C-OMe), 132.7 (s, Ar$C-CH_2OH$), 131.9, 131.2 (s, 1-C, 1'-C), 120.8 (d, 6'-H), 113.0 (d, 3-C), 112.4, 111.7, 111.0 (d, 6-C, 2'-C, 5'-C), 61.2 (t, CH_2OH), 55.6, 55.4, 55.3 (q, 4 x MeO), 47.6 (d, CHCO), 38.46 (t, CH_2-CH).

I.R. (0.5% $CHBr_3$). ν_{max}, 3580 (OH), 3480, 3380 (NH_2), 1675 (C=O) cm^{-1}.

U.V. λ_{max} (ε) nm. 232 (15500), 281.5 (5700).

Mass, m/e 375 (M^+, 36%), 358 (100), 313 (20), 209 (16), 151 (93).

Found: C, 63.85; H, 6.71; N, 3.62. $C_{20}H_{25}NO_6$ requires: C, 63.98; H, 6.71; N, 3.73%.

3-(3,4-Dimethoxyphenyl)-3-(2-acetoxymethyl-4,5-dimethoxyphenyl)propionamide (54).

3-(3,4-Dimethoxyphenyl)-2-(2-hydroxymethyl-4,5-dimethoxyphenyl)propionamide (53) (2.04 g, 0.005 mol) in dry pyridine (80 cm^3) was treated with acetic anhydride (0.62 g, 0.006 mol). After standing at room temperature for 3 days water (10 cm^3) was added and the solution evaporated to a yellow oil which was dissolved in ethyl acetate (20 cm^3). The organic layer was washed with water (2 x 20 cm^3), dried (Na_2SO_4) and evaporated to an off white solid. This solid was recrystallised from ethyl acetate/petroleum ether to furnish colourless needles (2.0 g, 83%).

m.p. 139°C.

^1H n.m.r. (90 MHz, $CDCl_3$). δ 7.1 (s, 1H, 6-H), 6.73 (s, 1H, 3-H), 6.7 (d, 1H, 5'-H, J=6Hz), 6.55 (dd, 1H, 6'-H, J=6, 2Hz), 6.4 (d, 1H, 2'-H, J=2Hz), 6.05, 5.45 (2 x br.s, 2H, NH_2), 4.65 (AB, 2H, CH_2OAc), 4.0, 3.35, 2.85 (ABX, 3H, CH_2-CH, J=15, 9, 6Hz), 3.9, 3.85, 3.8, 3.68 (4s, 12H, 4 x MeO), 2.0 (s, 3H, CH_3CO).

^{13}C n.m.r. ($CDCl_3$). δ 175.6 (s, NC=O), 170.9 (s, MeC=O), 149.9, 148.6, 148.1, 147,5 (s, C-OMe), 132.0, 126.2 (s, 1-C, 2-C, 1'-C), 121.0 (d, 6'-C), 113.2 (d, 3-C), 112.6, 111.3,

110.1 (d, 6-C, 2'-C, 5'-C), 63.8 (t, $\underline{C}H_2OAc$), 56.0, 55.8, 55.6 (q, 4 x MeO), 48.7 (d, $\underline{C}H-CH_2$), 39.3 (t, $\underline{C}H_2-CH$), 20.9 (q, $\underline{Me}CO$).

I.R. (0.5% $CHBr_3$). ν_{max} 3490/3380 (NH_2), 1727 (ester), 1680 (amide) cm^{-1}.

Mass m/e 417 (M^+, 7%), 357 (9), 313 (28), 206(11), 151 (100).

Found: C, 63.20; H, 6.56; N, 3.22. $C_{22}H_{27}NO_7$ requires: C, 63.30; H, 6.52; N, 3.36%.

3-(3,4-Dimethoxyphenyl)-2-(2-benzyloxymethyl-4,5-dimethoxyphenyl)propionamide (59).

Sodium hydride (0.16 g, 0.003 mol) and dry 1,2-dimethoxyethane (DME) (15 cm^3) was stirred at 0°C under a dry nitrogen atmosphere. 3-(3,4-dimethoxyphenyl)-2-(2-hydroxymethyl-4,5-dimethoxyphenyl)propionamide (53) (1.1 g, 0.003 mol) in the minimum volume of dry DME was added dropwise over 0.25h. the mixture was stirred at 0°C for 2h. then benzyl bromide (0.55 g, 0.003 mol) in dry DME (5 ml) was added. The solution was stirred at room temperature for 3 days, filtered and evaporated to yield a light brown oil, which was chromatographed over silica using dichloromethane/absolute ethanol (20:1) as the eluant. This procedure produced the title compound as a white solid (0.8 g, 59%).

m.p. 102 - 104°C.

^1H n.m.r. (90MHz, $CDCl_3$). δ 7.3 (s, 5H, phenyl group), 7.0, 6.6 (2s, 2H, 3-H, 6-H), 6.63 (d, 1H, 5'-H), 6.45 (dd, 1H, 6'-H), 6.4 (d, 1H, 2'-H), 6.25, 5.0 (2 x br.s, 2H, NH_2), 4.45 (AB, 2H,

$OC\underline{H}_2Ph$, $\underline{J}$=12Hz), 4.15 (AB, 2H, $C\underline{H}_2OCH_2Ph$, $\underline{J}$=12Hz), 3.87, 3.8, 3.77, 3.63 (4s, 12H, 4 x MeO), 3.80, 3.35, 2.8 (ABX, 3H, $C\underline{H}_2$-$C\underline{H}$, $\underline{J}$=14, 6).

I.R. (0.5% $CHBr_3$). ν_{max}, 3480, 3340, (NH), 1680 (amide) cm^{-1}.

Mass, m/e 465 (M^+, 3%), 358 (5), 313 (23), 179 (9), 151 (100).

Found: C, 69.52; H, 6.73; N, 2.87. $C_{27}H_{32}NO_6$ requires: C, 69.51; H, 6.91; N, 3.0%.

3-(3,4-Dimethoxyphenyl)-2-(2-hydroxymethyl-4,5-dimethoxyphenyl)-N-methyl propionamide (61)

4-(3,4-Dimethoxybenzyl)-6,7-dimethoxyisochroman-3-one (1) (11.2 g, 0.03 mol) in 33% methylamine in ethanol (250 cm^3) was heated at reflux for 4h. The cooled solution was evaporated to a white solid which was recrystallised from ethanol to form colourless prisms (7.8 g, 65%).

m.p. 146°C, (lit.[3], 146-148°C).

^1H n.m.r. (90MHz, $CDCl_3$). δ 7.1 (s, 1H, 6-H), 6.75 (br.s, 1H, NH), 6.65 (m, 3H, 2'-H, 5'-H, 6'-H), 6.5 (s, 1H, 3-H), 4.4 (AB, 2H, $C\underline{H}_2OH$, $\underline{J}$=12Hz), 3.9, 3.6 - 2.8 (ABX, 3H, $C\underline{H}_2$-$C\underline{H}$), 3.88, 3.78, 3.67 (s, 12H, 4 x MeO), 3.3 (br.s, 1H, OH, removed by D_2O), 2.56 (d, 3H, NMe, $\underline{J}$=5Hz).

^{13}C n.m.r. (DMSO). δ 173.0 (s, C=O), 148.4, 147.8, 147.2 (s, $\underline{C}$-OMe), 132.7, 132.1, 131.1 (s, 1-C, 2-C, 1'-C), 120.8 (d, 6'-C), 113.0 (d, 3-C), 112.4, 111.8, 111.4 (d, 6-C, 2'-C, 5'-C), 61.1 (t, $\underline{C}H_2OH$), 55.7, 55.5, 55.4 (q, 4 x MeO), 48.0 (d, $\underline{C}H$-CH_2), 38.6 (t, $\underline{C}H_2$-CH), 25.6 (q, NMe).

I.R. ν_{max}, 3540 - 3000 (OH), 3380 (NH), 1650 (amide) cm^{-1}

U.V. λ_{max} (ε) nm, 285 (3815).

Mass, m/e, 389 (M^+, 10%), 371 (15), 313 (100).

Found: C, 64.62; H, 6.98; N, 3.77. Calc. for $C_{21}H_{27}NO_6$: C, 64.8; H, 7.0; N, 3.6%.

3-(3,4-Dimethoxyphenyl)-2-(2-acetoxymethyl-4,5-dimethoxyphenyl)-N-methylpropionamide (62).

3-(3,4-Dimethoxyphenyl)-2-(2-hydroxymethyl-4,5-dimethoxyphenyl)-N-methylpropionamide (61) (2.21 g, 0.006 mol) and acetic anhydride (0.59 g, 0.006 mol) in dry pyridine (30 cm^3) were left to stand at room temperature for 3 days. Water (10 cm^3) was added and the solution evaporated to a yellow oil, which was dissolved in ethyl acetate (25 cm^3) then washed with 1N hydrochloric acid (2 x 50 cm^3), water (50 cm^3) and finally dried (Na_2SO_4). Evaporation of the solvent left an off white solid which was crystallised from ethyl acetate/petroleum ether to form colourless prisms (1.8 g, 73%).

m.p. 125 - 127°C.

^{1}H n.m.r. (90 MHz, $CDCl_3$), δ, 7.1 (s, 1H, 6-H), 6.8 - 6.4 (m, 4H, 3-H, 2'-H, 5'-H, 6'-H), 6.0 (br.q, 1H, NH), 4.67 (AB, 2H, CH_2OAc, J=12Hz), 3.9, 3.83, 3.80, 3.7 (4s, 12H, 4 x MeO), 3.9, 3.5 - 2.8 (ABX, 3H, CH_2-CH), 2.7 (d, 3H, N-Me, J=7Hz), 2.0 (s, 3H, MeCOO).

^{13}C n.m.r. ($CDCl_3$). δ 173.6 (s, NCO), 170.8 (s, MeCOO), 149.8, 148.7, 147.9, 147.5 (s, 4 x MeO-C), 132.4, 132.2 (s, 1-C, 1'-C), 126.0 (s, 2-C), 121.0 (d, 6'-C), 113.3 (d, 3-C), 112.6, 111.4, 110.4 (d, 6-C, 2'-C, 5'-C), 63.8 (t, CH_2OAc), 56.0, 55.8, 55.7 (q, 4 x MeO), 49.4 (d, CH-CH_2), 39.7 (t, CH_2-CH), 26.3

(q, NMe), 20.9 (q, MeCOO).

I.R. (0.5% $CHBr_3$). ν_{max}, 3430, 3400 (NH), 1725, (OAc), 1665, 1510 (Amide).

Mass, m/e 431 (M^+, 2%), 370 (28), 312 (90), 151 (100).

Found: C, 64.15; H, 6.92; N, 3.44. $C_{23}H_{29}NO_7$ requires: C, 64.02; H, 6.77; N, 3.25%.

2,3,6,7-Tetramethoxy-N-methylphenanthrene-9-carboxamide (63).

A solution of 3-(3,4-dimethoxyphenyl)-2-(2-acetoxymethyl-4,5-dimethoxyphenyl)-N-methylpropionamide (62) (1 g, 0.0023 mol) in dry dichloromethane/acetonitrile (1:1, v/v) (16 cm^3) was cooled under a dry nitrogen atmosphere to -8°C. Vanadium trifluoride oxide (1.2 g, 0.009 mol) in dry acetonitrile (30 cm^3) was slowly added and the resultant mixture stirred for 3.5 h. Citric acid (7.5 g) in water(50 cm^3) was added followed by water (200 cm^3) and the organic phase was separated. The aqueous phase was extracted with dichloromethane (4 x 25 cm^3) and the combined organic extracts washed with water (20 cm^3) and dried (Na_2SO_4). Removal of the solvent left a brown tar which was chromatographed over silica using 1% absolute ethanol in dichloromethane as the eluant. This process gave the title compound as an off white solid after crystallisation from ethyl acetate/petroleum ether (0.02 g, 2.5%).

^1H n.m.r. (90 MHz, $CDCl_3$). δ, 8.0 (br.q, 1H, CONHMe), 7.9 - 7.68 (4s, 4H, 1-H, 4- H, 5-H, 8-H), 7.2 (s, 1H, 10-H), 4.1, 3.98 (2s, 12H, 4 x MeO), 3.0 (d, 3H, NHMe, J=8Hz).

I.R. ν_{max}, 3400 (NH), 1650 (amide), 1610 cm^{-1}.

U.V. λ_{max} nm, 262, 288.

3-Benzyloxy-4-methoxybenzaldehyde (73).

3-Hydroxy-4-methoxybenzaldehyde (72) (20 g, 0.13 mol), benzyl chloride (18 cm^3), anhydrous potassium carbonate (10 g) and absolute methanol (45 cm^3) were refluxed for 6 h. The cooled mixture was then filtered and the solid washed with water and recrystallised from methanol. The filtrate was cooled to 0^oC and the crystals were recrystallised from methanol to yield colourless needles (27.5 g, 86%).

m.p. 62^oC, (lit.[43], 63^oC).

^1H n.m.r. (90 MHz, $CDCl_3$). δ 9.85 (s, 1H, CHO), 7.25 - 7.60 (m, 7H, 2-H, 5-H, Ph), 7.01 (d, 1H, 5-H, J=8Hz) 5.18 (s, 2H, CH_2-Ph), 3.92 (s, 3H, MeO).

^{13}C n.m.r. (DMSO). δ 191.0 (d, CHO), 154.7 (s, 3-C), 148.3 (s, 4-C), 136.7 (s, 1'-C), 129.8 (s, 1-C), 128.4 (d, 3'-C, 5'-C), 127.9 (d, 2'-C, 6'-C), 127.7 (d, 4'-C), 126.2 (d, 6-C), 111.5 (d, 2-C, 5-C), 70.1 (t, OCH_2-Ph), 55.9 (q, MeO).

I.R. ν_{max}, 1683 (CHO) cm^{-1}.

U.V. λ_{max} (ε) nm, 230.5 (21700), 275 (11000), 307 (8400).

Mass, m/e, 242 (M^+, 18%), 91 (100).

Found: C, 74.38; H, 5.81. Calc. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.83%.

3-Benzyloxy-4-methoxybenzylalcohol (74).

3-Benzyloxy-4-methoxybenzaldehyde (73) (23.1 g, 0.095 mol) in methanol (400 cm^3) was treated with sodium borohydride (10 g, 0.26 mol) in portions over a period of 0.5 h. The mixture was stirred for 20 h. and then 2N hydrochloric acid (150 cm^3) and water (300 cm^3) were added. After extraction with chloroform (3 x 100 cm^3) the combined organic extracts were washed with water (2 x 200 cm^3) and dried ($MgSO_4$). Evaporation of the solvent left a light brown oil which slowly crystallised on cooling, recrystallisation from methanol yielded a white solid (17.0 g, 73%).

m.p. 72 - 73°C, (lit.[45], 73°C).

^{1}H n.m.r. ($CDCl_3$). δ 7.34 (m, 5H, benzyl group), 6.9 (s, 1H, ArH, 2-H), 6.8 (s, 2H, 2 x ArH, 5-H and 6-H), 5.06 (s, 2H, $PhC\underline{H}_2OAr$), 4.45 (s, 2H, $ArC\underline{H}_2OH$), 2.80 (s, 3H, MeO), 2.06 (br.s, 1H, OH removed by D_2O).

^{13}C n.m.r. (DMSO). δ 148.2 (s, 3-C), 147.8 (s, 4-C), 137.3 (s, 1'-C), 135.2 (s, 1-C), 128.2 (d, 3'-C, 5'-C), 127.6 (d, 2'-C, 4'-C, 6'-C), 119.2 (d, 6-C), 112.7 (d, 2-C), 112.1 (d, 5-C), 70.1 (t, $O\underline{C}H_2Ph$), 62.8 (t, $\underline{C}H_2OH$), 55.7 (q, MeO).

I.R. ν_{max}, 3200 (OH) cm^{-1}.

Mass, m/e 244 (M^+, 18%), 91 (100).

Found: C, 73.99; H, 6.66. Calc. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60%.

3-Benzyloxy-4-methoxybenzylchloride (75).

An ice cold solution of 3-benzyloxy-4-methoxybenzyl alcohol (74) (5.07 g, 0.02 mol) in dry chloroform (200 cm^3) had freshly distilled thionyl chloride (2 cm^3) added dropwise over a period of 0.25 h. After stirring at 0^oC for 1 h. the solution was carefully added to cold water (100 cm^3) and the organic phase separated. The organic layer was washed with saturated sodium bicarbonate solution (2 x 100 cm^3), water (100 cm^3), and finally dried ($MgSO_4$). Evaporation of the solvent left a light yellow oil which crystallised on standing, and was recrystallised from dichloromethane/petroleum ether to yield white plates (5.0 g, 92%).

m.p 69 - 70^oC, (lit.[45], 77^oC).

^1H n.m.r. ($CDCl_3$). δ, 7.37 (m, 5H, 5 x ArH, benzyl group), 6.88 (m, 2H, 5-H, 6-H), 6.84 (s, 1H, 2-H), 5.12 (s, 2H, OCH_2Ph), 4.48 (s, 2H, CH_2-Cl), 3.84 (s, 3H, MeO).

^{13}C n.m.r. ($CDCl_3$). δ 150.2 (s, 3-C), 148.5 (s, 4-C), 137.0 (s, 1'-C), 130.1 (s, 1-C), 128.5 (d, 3'-C, 5'-C), 127.9 (d, 2'-C, 6'-C), 127.4 (d, 4'-C), 121.8 (d, 6-C), 115.0 (d, 2-C), 112.0 (d, 5-C), 71.2 (t, OCH_2Ph), 56.0 (q, MeO), 46.4 (t, CH_2Cl).

I.R. ν_{max}, 1610, 1590 cm^{-1}.

Mass, m/e 264 (M^+, 29%), 262 (M^+, 64), 228 (11), 136 (23), 91 (100).

3-Benzyloxy-4-methoxybenzylcyanide (76).

3-Benzyloxy-4-methoxybenzylchloride (75) (2.36 g, 0.008 mol) and sodium cyanide (0.6 g, 0.012 mol) were dissolved in dry N,N-dimethylformamide (40 cm^3) and stirred at room temperature for 20 h. The mixture was poured into water (40 cm^3) and extracted with benzene (4 x 50 cm^3). The combined organic extracts were washed with water (3 x 60 cm^3), dried ($MgSO_4$) and evaporated to an off white solid which was crystallised from methanol to afford colourless prisms (2.04 g, 90%).

m.p 72 - 73°C (lit.[46], 80°C).

^{1}H n.m.r. ($CDCl_3$). δ, 7.53 - 7.1 (m, 5H, 5 x ArH, benzyl group), 6.84 (s, 3H, 2-H, 5-H, 6-H), 5.1 (s, 2H, $ArOCH_2Bn$), 3.84 (s, 3H, MeO), 3.59 (s, 2H, CH_2-CN).

^{13}C n.m.r. ($CDCl_3$). δ 150.4 (s, 3-C), 148.7 (s, 4-C), 136.8 (s, 1'-C), 128.5 (d, 3'-C, 5'-C), 127.9 (d, 2'-C, 6'-C), 127.4 (d, 4'-C), 122.3 (s, 1-C), 120.9 (d, 6-C), 117.9 (s, C≡N), 114.1 (d, 2-C), 112.4 (d, 5'-C), 71.3 (t, $PhCH_2O$), 56.1 (q, MeO), 23.0 (t, CH_2CN).

I.R. ν_{max}, 2240 (C≡N) cm^{-1}

Mass, m/e 253 (M^+, 13%), 117 (4), 91 (100).

Found: C, 74.66; H, 5.90; N, 3.47. Calc. for $C_{16}H_{15}NO_2$: C, 74.80; H, 5.77; N, 3.49%.

α-(3,4-Dimethoxyphenyl)-3-benzyloxy-4-methoxycinnamonitrile (77).

Sodium methoxide in methanol (sodium (0.3 g) in dry methanol (30 cm^3)) was added dropwise to an ice cold solution of 3-benzyloxy-4-methoxybenzylcyanide (76) (1.52 g, 0.006 mol) and 3,4-dimethoxybenzaldehyde (9) (1.05 g, 0.006 mol) in dry methanol (80 cm^3). The solution was stirred at room temperature for 30 h. The yellow precipitate was removed by filtration and crystallised from methanol to yield fine yellow needles (1.6 g, 66%).

m.p. 82 - 84°C.

^{1}H n.m.r. ($CDCl_3$). δ 7.6 (d, 1H, 6'-H, J=2Hz), 7.54 - 7.05 (m, 10H, 9 x ArH, vinylic), 6.82 (dd, 1H, 5-H, J=6, 2Hz), 5.13 (br.s, 2H, OCH_2Ph), 3.90, 3.85 (2s, 9H, 3 x MeO).

^{13}C n.m.r. ($CDCl_3$). δ 151.0, 149.1, 148.6 (s, 3-C, 4-C, 3'-C, 4'-C), 140.2 (s, ArCCN), 136.9 (s, 1-Ph), 128.6 (d, 3-Ph, 5-Ph), 128.0 (d, 2-Ph, 6-Ph), 127.6 (d, 4-Ph), 127.0, 118.6 (s, 1-C, 1'-C), 124.0 (d, 6'-C), 119.4 (d, 6-C), 118.6 (d, C=CHAr), 112.2, 112.1, 111.2, 111.1 (d, 2-C, 5-C, 2'-C, 5'-C), 108.4 (s, C≡N), 71.5 (t, $PhCH_2O$), 56.0, 55.9 (q, 3 x MeO).

I.R. ν_{max}, 2200 (C≡N) cm^{-1}

U.V. λ_{max} (ε) nm. 250 (13000), 360 (20400).

Mass, m/e 401 (M^+, 27%), 91 (100).

Found: C, 74.66; H, 5.90; N, 3.47. $C_{25}H_{23}NO_4$ requires: C, 74.80; H, 5.77; N, 3.49%.

7-Benzyloxy-9-cyano-2,3,6-trimethoxyphenanthrene (78).

A solution of α-(3,4-dimethoxyphenyl)-3-benzyloxy-4-methoxycinnamonitrile (77) (1.22 g, 0.003 mol) in dry dichloromethane (30 cm^3) and dry acetonitrile (30 cm^3). After cooling to $-14^{\circ}C$ vanadium trifluoride oxide (3.76, 0.03 mol) in dry acetonitrile (100 cm^3) was added over a period of 0.25 h. The resultant mixture was stirred at -12° for 2h., then citric acid (15 g), in water (100 cm^3) was added and the organic layer separated. The aqueous layer was extracted with dichloromethane (2 x 50 cm^3) and the combined organic extracts were washed with brine (2 x 100 cm^3) and dried ($MgSO_4$). Evaporation of the solvent yielded a yellow solid, which was chromatographed over neutral alumina using dichloromethane as the eluant, to afford a white solid. This solid was crystallised from benzene to furnish white needles (1.0 g, 83%).

m.p. $232^{\circ}C$.

^1H n.m.r. ($150^{\circ}C$., DMSO), δ, 8.13 - 7.94 (m, 3H, 4-H, 5-H, 8-H), 7.66 - 7.24 (m, 8H, 1-H, 10-H, $\underline{Ph}CH_2O$), 5.34 (s, 2H, $PhC\underline{H}_2O$), 4.12 (s, 6H, 2 x MeO), 3.98 (s, 3H, MeO).

I.R. ν_{max}, 2210 (C≡N), 1618 cm^{-1}.

U.V. λ_{max} (ε) nm. 266 (10270), 279 (5770), 290 (6280), 366 (2460).

Mass, m/e, 399 (M^+, 44%), 308 (61), 91 (100).

4-(3-Benzyloxy-4-methoxybenzylidene)-2-phenyl-5(4H)-oxazolone (80).

3-Benzyloxy-4-methoxybenzaldehyde (73) (5 g, 0.02 mol.), hippuric acid (3.77 g, 0.02 mol), anhydrous sodium acetate (1.7 g) and acetic anhydride (13 cm^3) were heated on a steam bath for 1 h. The mixture was then cooled and added to water (200 cm^3) from which a solid separated. This solid was washed with water (200 mL) prior to crystallisation from ethyl acetate/petroleum ether. This procedure eventually gave a yellow amorphous solid (6.1 g, 80%).

m.p. 150°C, (lit.[44], 155°C).

^{1}H n.m.r. (90MHz, $CDCl_3$). δ 8.2 - 8.0 (m, 3H, 3 x ArH, 6-H (benzylidine) + 2-H, 6-H (2-phenyl sub.)), 7.7 - 7.3 (m, 9H, rest of aromatics), 7.18 (s, 1H, vinyl), 6.98 (d, 1H, ArH, 5-H (benzylidene), J=9Hz), 5.3 (s, 2H, OCH_2-Ph), 3.95 (s, 3H, MeO).

I.R. (0.5% $CHBr_3$). ν_{max} 1780, 1760 (C=O), 1645 (C=N) cm^{-1}.

U.V. λ_{max} (ε) nm. 265 (13900), 280(sh), 400 (32400).

Mass, m/e 385 (M^+, 22%), 105 (92), 91 (100).

Found: C, 74.75; H, 5.0; N, 3.51. Calc. for $C_{19}H_{24}NO_4$: C, 74.79; H, 4.97; N, 3.63%.

3-Benzyloxy-4-methoxyphenylpyruvic acid (81)

A suspension of 4-(3-benzyloxy-4-methoxybenzylidene)-2-phenyl-5(4H)-oxazolone (80) (5 g, 0.012 mol) in sodium hydroxide solution (2.5 mol dm^{-1}, 100 cm^3) was refluxed under a nitrogen atmosphere for 9 h. The cool solution was acidified with dilute hydrochloric acid and extracted with dichloromethane (3 x 30 cm^3). The combined organic extracts were extracted with sodium bicarbonate solution (5 x 10 cm^3), the combined aqueous extracts were acidified with dilute hydrochloric acid. The acidified aqueous solution was extracted with ethyl acetate (3 x 20 cm^3),

evaporation of the solvent left an off white solid which was crystallised from ethanol to afford white needles (1.3 g, 40%).

m.p. 153 - 155°C, (lit.[44], 160 - 161°C).

^{1}H n.m.r. (90MHz, $CDCl_3$/(DMSO 3 drops)). δ, 8.9 (br.s, 2H, COOH, enolic OH), 7.65 - 7.15 (m, 7H, 2-H, 6-H, CH_2Ph), 6.89 (d, 1H, 5-H, J=9Hz), 6.42 (s, 1H, vinyl), 5.11 (s, 2H, PhCH_2O), 3.86 (s, 3H, MeO).

I.R. ν_{max}, 3460 (OH), 2800 - 2500 (OH), 1690 (COOH), 1600 cm^{-1}.

Mass, m/e 300 (M^+, 10%), 91 (100).

N-Benzoyl-2-(3-benzyloxy-4-methoxybenzylidene)glycine (82).

4-(3-Benzyloxy-4-methoxybenzylidene)-2-phenyl-5(4H)-oxazolone (80) (0.52 g, 0.0014 mol) was added to a solution of potassium hydroxide (0.67 g, 0.011 mol) in ethanol (50 cm^3), and water (8 cm^3), the suspension was then heated at reflux for 1.5 h. under a nitrogen atmosphere. The cooled solution was acidified with 2N hydrochloric acid and the solid collected by filtration. Crystallisation of the solid from ethyl acetate gave white needles (0.31 g, 55%).

m.p. 224°C (dec.).

^{1}H n.m.r. (90MHz, DMSO). δ, 9.95 (br.s, 1H, COOH), 8.1 (m, 2H, 2'-H, 6'-H), 7.55 (dd, 1H, 6-H, J_{ortho}=9Hz), 7.5 (s, 1H, vinyl), 7.7 - 7.1 (m, 4H, 2-H, 3'-H, 4'-H, 5'-H), 7.0 (d, 1H, 5-H, J=9Hz), 4.9 (s, 2H, PhCH_2O), 3.8 (s, 3H, MeO).

I.R. ν_{max}, 3215 (NH), 2800 - 2500 (OH), 1690 (COOH), 1650, 1620 (amide) cm^{-1}

U.V. λ_{max} (ε) nm, 226 (sh), 319 (13400).

Mass, m/e 403 (M^+, 15%), 105 (42), 91 (100).

2-(3-Benzyloxy-4-methoxyphenyl)acetic acid (83).

An ice cold solution of 3-(3-benzyloxy-4-methoxyphenyl) pyruvic acid (81) (4.4 g, 0.014 mol) in 2% potassium hydroxide solution (60 cm^3) had hydrogen peroxide solution (6 cm^3) added dropwise. After standing for 3 days at room temperature the solution was extracted with dichloromethane (2 x 30 cm^3), acidified with 2N hydrochloric acid and extracted with ethyl acetate (3 x 100 cm^3). The combined ethyl acetate extracts were dried ($MgSO_4$) and evaporated to an off white solid which was crystallised from benzene to colourless prisms (3.61 g, 93%).

m.p. 120 - 122°C, (lit.[49], 125°C).

^{1}H n.m.r. (90MHz, $CDCl_3$). δ, 11.2 (br.s, 1H, COOH), 7.5 (m, 5H, $ArOCH_2\underline{Ph}$), 6.87 (s, 3H, 2-H, 5-H, 6-H), 5.12 (s, 2H, $C\underline{H}_2Ph$), 3.84 (s, 3H, MeO), 3.52 (s, 2H, $C\underline{H}_2COOH$).

I.R. ν_{max}, 2670 (OH), 1710 (COOH) cm^{-1}.

U.V. λ_{max} (ε) nm. 232 (7107), 283 (2281).

Mass, m/e, 272 (M^+, 22%), 91 (100).

Found: C, 70.87; H, 5.91. Calc. for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92%.

Methyl-(3-benzyloxy-4-methoxyphenyl)acetate (84).

An ice cold solution of (3-benzyloxy-4-methoxyphenyl)-acetic acid (83) (0.59 g, 0.002 mol) in dry ether (30 cm^3) had excess diazomethane in dry ether added until the yellow colour persisted. After 0.25 h. at 0°C glacial acetic acid (2 cm^3) was carefully added dropwise. The solution was evaporated and the resultant yellow oil chromatographed over silica using dichloromethane as the eluant to yield a white solid (0.49 g, 79%).

m.p. 79 - 81°C.

^{1}H n.m.r. (90MHz, $CDCl_3$). δ 7.4 (m, 5H, phenyl group), 6.85 (s, 3H, 3 x ArH, 2-H, 5-H, 6-H), 5.1 (s, 2H, OCH_2Ph), 3.85 (s, 3H, MeO), 3.65 (s, 3H, COOMe), 3.5 (s, 2H, CH_2COOMe).

I.R. (0.5% $CHBr_3$). ν_{max}, 1730 (ester) cm^{-1}.

Mass, m/e 286 (M^+, 100%), 227 (29), 195 (27), 107 (42).

Found: C, 71.28; H, 6.35. $C_{17}H_{18}O_4$ requires: C, 71.31; H, 6.34%.

Attempted condensation between 3,4-dimethoxybenzaldehyde (9) and Methyl-(3-benzyloxy-4-methoxyphenyl)acetate (84).

Sodium methoxide in methanol (sodium (0.1 g) in dry methanol (20 mL)) had 3,4-dimethoxybenzaldehyde (9), (0.26, 0.0015 mol) in the minimum volume of dry methanol added dropwise. The ester (84) (0.4 g, 0.0014 mol) in the minimum volume of dry methanol was added dropwise over a period of 0.25 h. This mixture was stirred under a dry nitrogen atmosphere for 24 h, then dilute sulphuric acid (3 cm^3) was carefully added. The resultant solution was evaporated to near dryness, water (10 cm^3) was added and the mixture extracted with dichloromethane (4 x 15 cm^3). The combined organic extracts were washed with water (3 x 15 cm^3) and dried (Na_2SO_4). Evaporation of the solvent left an off white solid, which was shown to be a mixture of starting materials (^{1}H n.m.r., I.R., T.L.C.).

Bis-6',6'-(4-(3,4-dimethoxybenzyl)-6,7-dimethoxyisochroman-3-onyl) (86).

A solution of 4-(3,4-dimethoxybenzyl)-6,7-dimethoxyisochroman-3-one (1) (3.3 g, 0.009 mol) in dry dichloromethane (12 cm^3) was cooled to -10°C. Vanadium trifluoride oxide (3 g, 0.024 mol) in dry acetonitrile (40 cm^3) was slowly added in portions and the mixture was stirred at -10°C for 5.5 h. Citric acid (20 g) in water (200 cm^3) was added and the organic phase was separated, the aqueous phase was extracted with dichloromethane (3 x 50 cm^3). The combined organic extracts were washed with brine (2 x 100 cm^3) and dried ($MgSO_4$). Removal of the solvent by evaporation left a black tar, which was chromatographed over silica using ethyl acetate/cyclohexane (9:1, v/v) as the eluant. This process gave 9,8a-carbonyloxymethano-6,8a,9,10-tetrahydro-2,3,7-trimethoxy-6-oxophenanthrene (90) (0.026 g, 1%) identical to a sample prepared by the electrochemical oxidation of substrate (1).

The major product was a white solid (0.48 g, 7%) which proved to be a mixture of diastereomers of the title compound. A partial separation was achieved by repeated recrystallisation of the mixture from ethyl acetate.

Diastereomer 1.

^1H n.m.r. (90MHz, $CDCl_3$). δ, 6.37, 6.56, 6.28 (3s, 8H, 8 x ArH), 4.9 (s, 4H, 2 x Ar$\underline{CH}_2$O), 3.89, 3.85, 3.80, 3.72 (4s, 24H, 8 x MeO), 3.6 (m, 2H, 2 x $\underline{CH}$-CH_2), 2.79 (d, 4H, 2 x $\underline{CH}_2$-CH, $\underline{J}$=12Hz).

I.R. ν_{max}, 1740 (lactone) cm^{-1}.

Mass, m/e, 714 (M^+, 17%), 507 (45), 461 (37), 299 (100).

Diastereomer 2.

^1H n.m.r. (90MHz, $CDCl_3$). δ, 6.8, 6.48, 5.8, 5.75 (4s, 8H, 8 x ArH), 4.9, 4.65 (AB, 4H, $ArCH_2O$, J=12Hz), 3.9, 3.82, 3.68, 3.55 (4s, 24H, 8 x MeO), 3.4 (m, 2H, 2 x $CH-CH_2$), 3.0 - 2.7 (m, 4H, 2 x CH_2-CH).

I.R. ν_{max}, 1740 (lactone) cm^{-1}.

Mass, m/e, 714 (M^+, 13%), 507 (37), 461 (31), 299 (100).

9,8a-Carbonyloxymethano-6,8a,9,10-tetrahydro-2,3,7-trimethoxy-6-oxophenanthrene (90).

4-(3,4-Dimethoxybenzyl)-6,7-dimethoxyisochroman-3-one (1) (1.1 g, 0.003 mol) in 0.0001 mol cm^{-3} anhydrous sodium perchlorate in dry acetonitrile (110 cm^3), was electrolysed at an anode potential of 1.22V (vs SCE.) at 0°C using a platinum gauze electrode and a mercury pool cathode. After all the starting material had been oxidised ($\sim$ 2 h.), the anolyte was separated, water (10 cm^3) was added and the mixture evaporated to near dryness. The dark residue was dissolved in chloroform (100 cm^3), washed with water (50 cm^3), brine (40 cm^3) and dried ($MgSO_4$). After evaporation, the resultant oil was chromatographed over silica using ethyl acetate as the eluant to yield an off white solid. This was recrystallised from ethanol to furnish fine white needles (0.5 g, 48%).

m.p. 252°C, (lit.[2], 256 - 257°C).

^{1}H n.m.r. (250 MHz, $CDCl_3$). δ , 6.98 (s, 1H, 4-H, ArH), 6.79 (s, 1H, 1-H, ArH), 6.51 (s, 1H, 5-H), 6.00 (s, 1H, 8-H), 4.24, 3.98 (AB, 2H, 2 x 13-H, J=12.5Hz), 3.87 (s, 6H, 2 x MeOAr), 3.76 (s, 3H, 7-MeO), 3.20-3.00 (m, 3H, 9-H, 2 x 10-H), CH_2-CH).

^{1}H n.m.r. (250MHz, $CDCl_3$). Nuclear Overhauser effect experiment. Irradiation of δ 6.98 caused 20 - 25% enhancement of δ 6.51. Irradiation of δ 3.76 caused a 12% enhancement of δ 6.00 and vice versa, irradiation of δ 6.00 also caused a 9% enhancement of one of the resonances due to the methine proton α-to lactone carbon group (9-H) and a 4% intensification of the methine doublet at δ 4.24.

^{13}C n.m.r. (62.9MHz, $CDCl_3$/DMSO (1 drop)). δ 180.2 (s, 6-C, C=O), 177.7 (s, 11-C, lactone) 155.2, 151.6, 151.0, 149.0 (4 x s, 2-C, 3-C, 5a-C, 7-C), 128.0 (s, 10a-C), 126.0 (s, 4a-C), 124.2[a] (d, 8-C), 116.7 (d, 1-C), 111.2 (d, 4-C), 108.7[a] (d, 5-C), 77.0 (t, 13-C), 47.0 (s, 8a-C), 43.1 (d, 9-C), 28.9 (t, 10-C).

I.R. ν_{max}, 1760 (δ-lactone), 1660, 1650 (dienone), 1610 cm^{-1}.

U.V. λ_{max} (ε) nm, 265 (6650), 290 (4180), 360 (4750).

Mass, found: M^+, 342.1102. $C_{19}H_{18}O_6$ requires: M^+, 342.1101.

m/e, 342 (M^+, 100%), 284 (28), 266 (15), 253 (58).

Found: C, 66.3; H, 5.5. Calc. for $C_{19}H_{18}O_6$: C, 66.6; H, 5.3%.

9-Carboxamide-5,5a,6,7,8,8a,9,10-octahydro-6-hydroxy-8a-hydroxymethyl-2,3,7-trimethoxy-N-(n-propyl)phenanthrene (91).

Freshly distilled dry n-propylamine (1.42 g, 0.024 mol) in dry tetrahydrofuran (THF) (16 cm^3) was cooled to 0^oC under a dry nitrogen atmosphere. n-Butyl lithium in hexane (1.5 cm^3 (0.0016 mol cm^{-3}), 0.0024 mol) was added dropwise after stirring for 0.25 h, the hydroxy lactone (94) (0.24 g, 0.0007 mol) in dry THF (40 cm^3) was added in portions over a period of 0.25 h. The mixture was stirred overnight, then ammonium chloride (2.2 g) in water (10 cm^3) was added and the organic phase separated. The aqueous phase was extracted with ether (3 x 20 cm^3) and the combined organic extracts were washed with dilute hydrochloric acid (50 cm^3), water (50 cm^3) and dried (Na_2SO_4). Removal of the solvent left a white gum which was chromatographed over silica using dichloromethane/ethyl acetate to yield the title compound as a white solid which was crystallised from ethyl acetate (0.15 g, 51%).

m.p. 154-155°C.

^{1}H n.m.r. (250MHz, $CDCl_3$). δ , 6.66(s, 1H, 4-H), 6.54 (s, 1H, 1-H), 6.30 (t, 1H, NH, J=7Hz), 4.92 (dd, 1H, OH, J=10, 3Hz), 3.83 (s, 6H, 2-MeO, 3-MeO), 3.8 - 3.55 (m, 4H, 6-H(ax), 7-H(eq), CH_2OH), 3.52 (s, 3H, 7-MeO(ax)),3.4 - 3.2 (m, 3H, $NHCH_2$, 10-H(ax), J=17, 12.5Hz), 2.9 (dd, 1H, 10-H(eq), J=17, 6.5Hz), 2.76 (dd + d, 2H, 6-HO(eq), 8-H(eq)), 2.58 (br.d, 1H, 5a-H, J=13, 3Hz), 2.4 (dd, 1H, 9-H, J=12.5, 6.5Hz), 2.34 (dt, 1H, 5-H(eq), J=13, 3Hz), 1.65 (m, 3H, CH_2CH_2Me, 5-H(ax), J=13, 13Hz),

0.92 (m, 4H, CH_2-$\underline{CH}_3$, 8-H(ax)).

^{1}H n.m.r. (250MHz, $CDCl_3$). Nuclear Overhauser effect experiment. Irradiation of δ 6.66 (4-H) caused a 9% enhancement of the δ 2.34 (5-H(eq)) signal. Irradiation of δ 6.54 (1-H) caused an enhancement of the 10-Hax and 10-Heq signals at δ 3.4 - 3.2 and δ 2.9.

I.R. ν_{max}, 3440 (OH), 3250 (NH), 1640 (amide) cm^{-1}.

Mass, found: M^+, 407.2308. $C_{22}H_{33}NO_6$ requires: M^+, 407.2309.

m/e, 407 (M^+, 13%), 389 (18), 348 (100), 239 (15).

9-Carboxamide-5,5a,6,7,8,8a,9,10-octahydro-6-trifluoroacetyl-8a-trifluoroacetylmethyl-2,3,7-trimethoxy-N-(n-propyl)-phenanthrene.

^{1}H n.m.r. (250 MHz , $CDCl_3$). δ , 6.68 (s, 2H, 1-H, 4-H), 5.15 (dt, 1H, 6-H(ax)), 4.62, 4.35 (AB, 2H, $\underline{CH}_2OCOCF_3$), 4.0 - 3.8 (m, 8H, 2-MeO, 3-MeO, 7-H(eq), 9-H(eq)),3.7 (m, 2H, $NHCH_2$), 3.42 (s, 3H, 7-MeO), 3.22 (d, 2H, 10-H), 2.98 (br.d, 1H, 5a-H(ax)), 2.59 (m, 1H, 8-H(eq)), 2.5 (m, 1H, 5-H(eq)), 2.24 (m, 1H, 5-H(ax)), 1.66 (m, 2H, $\underline{CH}_2Me$), 1.48 (m, 1H, 8-H(ax)), 0.95 (t, 3H, $CH_2\underline{CH}_3$).

9,8a-Carbonyloxymethano-5,5a,6,7,8,8a,9,10-octahydro-2,3,7-trimethoxy-6-oxophenanthrene (93) and 9,8a-carbonyloxymethano-5,5a,6,7,8,8a,9,10-octahydro-6-hydroxy-2,3,7-trimethoxy-phenanthrene (94).

A suspension of 9,8a-carbonyloxymethano-6,8a,9,10-tetrahydro-2,3,7-trimethoxy-6-oxophenanthrene (90). (0.5 g, 0.0014 mol) in A.R. acetone (200 cm^3) was hydrogenated at a

pressure of 100 p.s.i. in the presence of 10% palladium on charcoal (0.5 g) for a period of 20 h. After filtration through kieselguhr the solution was evaporated to a colourless gum which was chromatographed over silica using ethyl acetate as the eluant. The early fractions contained keto-lactone (93) (0.12 g, 25%), which was crystallised from ethyl acetate to yield colourless prisms.

m.p. 175 - 177°C.

^{1}H n.m.r. (250 MHz , $CDCl_3$). δ , 6.79, 6.61 (2s, 2H, 1-H, 4-H), 4.8, 3.72 (AB, 2H, CH_2O, J=10Hz), 3.9, 3.88 (2s, 6H, 3-MeO, 4-MeO), 3.68 (t, 1H, 7-H, J=2.5, 4), 3.35 (s, 3H, 7-MeO(ax)), 3.2 - 2.7 (m, 6H, rest of aliphatics), 2.62 (ABX, 1H, 8(eq)-H, J=4.75, 2.5), 2.09 (ABX, 1H, 8(ax)-H, J=4.75, 4).

I.R. (0.5% $CHBr_3$). ν_{max}, 1760 (lactone), 1720 (C=O)cm^{-1}

Mass, m/e, 346 (M^+, 100%), 227 (6), 201 (8), 177 (12).

Found: C, 65.81; H, 6.42. $C_{19}H_{22}O_6$ requires, C, 65.88; H, 6.40%.

The later fractions contained the hydroxy-lactone (94) (0.36, 72%), which crystallised from ethyl acetate/petroleum ether to yield colourless prisms.

m.p. 157 - 159°C.

^{1}H n.m.r. (250 MHz, $CDCl_3$). δ, 6.77, 6.72 (2s, 2H, 1-H, 4-H), 4.36 (AB, 1H, J=10Hz), 3.50 (AB, 1H, J=10, 1Hz), 3.9, 3.88 (2s, 6H, 2-MeO, 3-MeO), 3.85 (m, 1H, 6-H(ax)), 3.7 (m, 1H, 7-H(eq), J=3,3,3Hz), 3.48 (s, 3H, 7-OMe(ax)), 3.05 (ABX, 1H, 10-H(eq), J=15,2Hz), 2.86 (ABX, 1H, 10-H(ax), J=15, 8Hz), 7.33 (ABX, 1H,

9-H, J=8,2Hz), 2.65 (s, 1H, OH, removed by D_2O), 2.56 (m, 1H, 8-H(eq), J=15, 3Hz), 2.54 (m, 1H, 5a-H(ax), J=12, 3Hz), 2.37 (m, 1H, 5-H(eq), J=13, 4, 3Hz), 1.75 (m, 1H, 5-H(ax), J = 13, 12, 12Hz), 1.64 (m, 1H, 8-H(ax), J=15, 3, 1Hz). (see p.80)

^{13}C n.m.r. ($CDCl_3$). δ 179.5 (s, C=O), 148.4, 147.9 (s, 2-C, 3-C), 130.8 (s, 10a-C), 127.9 (s, 4a-C), 111.9 (d, 1-C), 108.6 (d, 4-C), 79.6 (t, CH_2O), 73.6, 71.1 (d, 6-C, 7-C), 57.4, 56.2, 56.0 (q, 3 x MeO), 48.1 (d, 5a-C), 42.3 (s, 8a-C), 40.8 (d, 9-C), 36.8 (t, 5-C), 30.0 (t, 8-C), 28.7 (t, 10-C).

I.R. (0.5% $CHBr_3$). ν_{max}, 3550 (OH), 1762 (lactone) cm^{-1}.

U.V. λ_{max} nm, 228, 278, 282.

Mass, m/e, 248 (M^+, 100%), 201 (6), 177 (6).

Found: C, 65.32; H, 6.81. $C_{19}H_{24}O_6$ requires: C, 65.5; H, 6.94%.

9-Carbomethoxy-6-hydroxy-2,3,7-trimethoxy-9,10-dihydrophenanthrene (95).

A suspension of 9,8a-carbonyloxymethano-6,8a,9,10-tetrahydro-2,3,7-trimethoxy-6-oxophenanthrene (90) (0.1 g, 0.0003 mol) in methanol (10 cm^3) containing concentrated hydrochloric acid (1 cm^3) was heated at reflux for 4 h. The cooled solution was evaporated and the residue was covered with water (10 cm^3) and extracted with chloroform (2 x 15 cm^3). The combined organic extracts were washed with brine (10 cm^3), dried ($MgSO_4$) and evaporated to a yellow oil which crystallised from ethanol (0.072 g, 70%).

m.p. 169-170°C, (lit.[37], 170 - 171°C).

^{1}H n.m.r. ($CDCl_3$). δ 7.26 (s, 1H, 5-H), 7.14 (s, 1H, 8-H), 6.76, 6.72 (2s, 2H, 1-H, 4-H), 5.6 (s, 1H, OH), 3.92, 3.88 (2s, 9H, 3 x MeO), 3.75, 3.12 (ABX, 3H, 9-H, 2 x 10-H), 3.60 (s, 3H, MeOOC).

I.R. ν_{max}, 3430 (OH), 1730 (ester), 1690 cm^{-1}.

U.V. λ_{max} nm, 215, 287, 325.

Mass, m/e, 344 (M^+, 100%), 285 (75), 270 (34).

4-(3-Methoxybenzylidene)-6,7-dimethoxyisochroman-3-one (106).

6,7-dimethoxyisochroman-3-one (16) (15.1 g, 0.073 mol) and freshly distilled 3-methoxybenzaldehyde (105) (9.9 g, 0.073 mol. b.p. = 76°C at 1.0 mmHg) were dissolved in dry toluene (300 cm^3), pyrrolidine (2 cm^3) was then added. The mixture was heated under reflux using a Dean and Stark trap and a dry nitrogen atmosphere for a period of 8 h. The solution was allowed to stand overnight and the yellow crystals were removed by filtration followed by recrystallisation from ethanol to yield fine yellow needles (8.5 g, 36%).

m.p. 95°C.

^{1}H n.m.r. ($CDCl_3$). Mainly E-isomer[5]. δ, 7.76 (s, 1H, vinylic), 7.38 - 6.9 (m, 4H, 2'-H, 4'-H, 5'-H, 6'-H), 6.87 (s, 1H, 8-H), 6.73 (s, 1H, 5-H), 5.3 (s, 2H, $ArCH_2O$), 3.92, 3.75, 3.5 (3s, 12H 3 x MeO).

^{13}C n.m.r. (DMSO). δ 167.5 (s, C=O), 159.3 (s, 3'-C), 149.4, 147.8 (s, 6-C, 7-C), 135.9 (s, 1'-C), 135.1 (s, 4-C), 129.5 (d, 6'-C), 126.2 (s, 8a-C), 125.1 (s, 4a-C), 121.7, 121.4 (d, 5'-C, Ar-CH=C), 114.7, 110.1, 108.7 (d, 5-C, 8-C, 2'-C, 4'-C), 68.5 (t, $ArCH_2O$), 55.6, 55.0 (q, 3 x MeO).

I.R. ν_{max}, 1710 (lactone), 1608 cm^{-1}.

U.V. λ_{max} nm, 205, 240, 348.

Mass, m/e 326 (M^+, 100%), 208 (63), 146 (36).

Found: C, 69.92; H, 5.57. $C_{19}H_{18}O_5$ requires C, 69.93; H, 5.56%.

4-(3-Methoxybenzyl)-6,7-dimethoxyisochroman-3-one (107).

A solution of 4-(3-methoxybenzylidene)-6,7-dimethoxyisochroman-3-one (106) (2 g, 0.006 mol) in ethyl acetate (80 cm^3) was hydrogenated at atmospheric pressure in the presence of 10% palladium on charcoal (0.1 g) for 24 h. After filtration through kieselguhr, the solvent was removed by evaporation to leave a yellow gum, which was chromatographed over silica using dichloromethane as the eluant. This produced a colourless gum (1.9 g, 95%).

^1H n.m.r. ($CDCl_3$). δ, 7.13 (dd, 1H, 5'-H, J=10Hz), 6.85 - 6.39 (m, 4H, 8-H, 2'-H, 4'-H, 6'-H), 6.32 (s, 1H, 5-H), 4.92 (AB, 2H, $ArCH_2O$, J=14Hz), 3.85 (br,s., 4H, 1 x MeO, $ArCH_2CH$), 3.7 (s, 6H, 2 x MeO), 3.2 (m, 2H, $ArCH_2CH$).

^{13}C n.m.r. ($CDCl_3$). δ 172.3 (s, C=O), 159.6 (s, 3'-C), 149.1, 148.4 (s, 6-C, 7-C), 139.0 (s, 1'-C), 129.3 (d, 6'-C), 125.6 (s, 8a-C), 123.4 (s, 4a-C), 121.6 (d, 5'-C), 114.9 (d, 8-C), 112.5, 110.7, 107.8 (d, 5-C, 2'-C, 4'-C), 69.4 (t, $ArCH_2O$), 56.0, 55.8, 54.9 (q, 3 x MeO), 46.8 (d, $CH-CH_2$), 38.3 (t, CH_2-CH).

I.R. (film). ν_{max}, 2950, 2850, 1740 (lactone), 1610 cm^{-1}.

U.V. λ_{max} nm, 225, 280.

Mass, m/e, 328 (M^+, 27%), 283 (9), 207 (100), 179 (22), 151 (25), 121 (31).

10,11-Dihydro-5,11-(iminomethano)2,3,7,8-tetramethoxy-5H-dibenzo[a,d]cyclohepten-12-one (57) and 11-carboxamide-10,11-dihydro-2,3,7,8-tetramethoxy-5H-dibenzo[a,d]cycloheptene (58).

2-(2-Acetoxymethyl-3,4-dimethoxyphenyl)-3-(3,4-dimethoxyphenyl)propionamide (54) (1.47 g, 0.0035 mol) in dry dichloromethane/acetonitrile (1:1 v/v, 10 cm^3) was cooled to -10°C under a dry nitrogen atmosphere. Vanadium trifluoride oxide (0.5 g, 0.004 mol) in dry acetonitrile (10 cm^3) was added and the mixture stirred at 0°C for 6 h. and at room temperature for 2.5 days. Citric acid (15 g) in water (100 cm^3) was added and the organic phase separated. The aqueous phase was extracted with dichloromethane (3 x 30 cm^3) and the combined organic extracts were washed with water (100 cm^3) and dried (Na_2SO_4). Removal of the solvents left a brown solid, which was chromatographed over silica, using petroleum ether/dichloromethane/absolute ethanol (5:4:1) as the eluant, to give a white solid.

This solid was further chromatographed over alumina using chloroform. The early fractions contained the amide (58) (0.092 g, 8%).

m.p. 200 - 202°C.

^1H n.m.r. (90 MHz, $CDCl_3$/DMSO). δ 6.75 (s, 4H, 1-H, 4-H, 6-H, 9-H), 6.6 (br.s, 2H, $CONH_2$), 4.4 - 3.0 (m, 5H, $ArCH_2Ar$, CH_2-CH), 3.8 - 3.6 (4s, 12H, 4 x MeO).

I.R. (0.5% $CHBr_3$). ν_{max} 3510, 3400 (NH_2), 1670 (amide) cm^{-1}.

Mass, found: M^+ 357.1575. $C_{20}H_{23}NO_5$ requires: 357.1576.

m/e 313.1422 (Calc. for $C_{19}H_{21}O_4$, 313.1440) corresponds to the loss of [.CO-NH_2].

The late fractions from the chromatography yielded the lactam (57) (0.135 g, 11%).

m.p. 268 - 270°C (dec.).

^{1}H n.m.r. (90 MHz, $CDCl_3$/DMSO). δ 8.78 (d, 1H, CONH, removed by D_2O), 6.95, 6.88, 6.6 (3s, 4H, 1-H, 4-H, 6-H, 9-H), 4.95 (d, 1H, NH-CH), 3.9 - 3.8 (m, 13H, 4 x MeO, CH-CO), 3.4, 2.95 (ABX, 2H, CH_2-CH, J_{gem}=15Hz).

I.R. (0.5% $CHBr_3$). ν_{max} 3405 (NH), 1675 (C=O) cm^{-1}

Mass, found: M^+ 355.1399. $C_{20}H_{21}NO_5$ requires: 355.1420.

10,11-Dihydro-5,11-(iminomethano)-2,3,7,8-tetramethoxy-5H-dibenzo[a,d]cyclohepten-12-one (57).

A solution of 3-(3,4-dimethoxyphenyl)-2-(2-benzyloxymethyl-4,5-dimethoxyphenyl)propionamide (59) (0.18 g, 0.0004 mol) in dry dichloromethane (8 cm^3) was cooled to -10°C, under a dry nitrogen atmosphere. Vanadium trifluoride oxide (0.12 g) in dry acetonitrile (30 cm^3) was added and the resultant mixture stirred for 2.5 days at a temperature of 0°C - 2°C. Citric acid (15 g) in water (100 cm^3) was added and the solution extracted with ethyl acetate (5 x 20 cm^3). The combined extracts were washed with brine (2 x 20 cm^3) and dried (Na_2SO_4). Removal of the solvent by evaporation left a brown tar, which was chromatographed over silica using dichloromethane/absolute ethanol (10:1, v/v). This produced the title compound (57) as an off white solid identical with a sample prepared by the action of VOF_3 on acetate (54) (see p.135).

9-Aminomethyl-5,5a,6,7,8,8a,9,10-octahydro-6-hydroxy-8a-hydroxymethyl-2,3,7-trimethoxy-N-(n-propyl)phenanthrene (103).

9-Carboxamide-5,5a,6,7,8,8a,9,10-octahydro-6-hydroxy-8a-hydroxymethyl-2,3,7-trimethoxy-N-(n-propyl)phenanthrene (91) (0.14 g, 0.0003 mol) in dry tetrahydrofuran (THF) (22 cm^3) under a dry nitrogen atmosphere, was cooled to 0^oC. Diborane in THF (18 cm^3, 0.00025 mol. cm^{-3}, 0.0045 mol) was carefully added and the resultant solution heated at reflux for 9 h. After cooling to room temperature dilute hydrochloric acid (10 cm^3) was carefully added and the solution heated at reflux for 0.25 h. The cool solution was basified with dilute sodium hydroxide solution and extracted with chloroform (5 x 40 cm^3). The combined organic extracts were washed with brine (2 x 40 cm^3) and finally dried (Na_2SO_4). Removal of the solvent left a colourless gum, which was dissolved in dry toluene (10 cm^3), dry ether (20 cm^3) saturated with hydrogen chloride gas was added, the solid was collected by decantation and dried under high vacuum to give a white solid (0.8 g, 55%).

m.p. 140 - 142°C.

^{1}H n.m.r. (250 MHz, $CDCl_3$). δ 9.44 (br.s, 1H, NH), 6.64, 6.61 (2s, 2H, 1-H, 4-H), 4.23 (br.s, 1H, CH_2OH), 3.79, 3.73 (2s, 6H, 2 x MeO), 3.85 - 3.5 (m, 4H, 6-H(ax), 7-H(eq), CH_2OH), 3.47 (m, 3H, 7-OMe ax)),CH_2NH), 3.29 (m, 3H, NCH_2Et, 10-H(ax)),3.01 (m, 1H, 10 - H(eq)),2.73 (m, 2H, 8-H(eq)),6-OH), 2.55 (br.d, 1H, 5a-H), 2.26 (m, 1H, 9-H), 1.88(q, 2H, CH_2Me), 1.58 (q, 1H, 5-H(eq)), 1.14 (m, 1H, 5-H(ax)), 0.88 (t, 3H, $NCH_2CH_2CH_3$)

I.R. ν_{max} 3600 - 3200 (OH, NH), 1610 cm^{-1}.

Mass, found: M^+, 393.2517. $C_{22}H_{35}NO_5$ requires: M^+ 393.2519.

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